DIASTOLIC STRESS TEST-NOVEL MARKER TO DETECT CORONARY ARTERY DISEASE

A TISSUE DOPPLER ECHOCARDIOGRAPHIC STUDY

Dissertation Submitted for

D.M. DEGREE EXAMINATION
BRANCH II - CARDIOLOGY

STANLEY MEDICAL COLLEGE

and

GOVERNMENT STANLEY HOSPITAL
CHENNAI – 600001

THE TAMILNADU
DR.M.G.R. MEDICAL UNIVERSITY
CHENNAI

AUGUST – 2014

CERTIFICATE

This is to certify that the dissertation entitled **– "DIASTOLIC STRESS TEST- NOVEL MARKER TO DETECT CORONARY ARTERY DISEASE A TISSUE DOPPLER ECHOCARDIOGRAPHIC STUDY"** is the bonafide original work of Dr**. S. RAJESH KUMAR** in partial fulfillment of the requirements for D.M. Branch II (CARDIOLOGY) examination of THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY to be held on August 2014. The period of post graduate study and training was from August 2011 to July 2014

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DECLARATION

I **Dr. S. RAJESH KUMAR**, solemnly declare that this dissertation entitled **– "DIASTOLIC STRESS TEST- NOVEL MARKER TO DETECT CORONARY ARTERY DISEASE A TISSUE DOPPLER ECHOCARDIOGRAPHIC STUDY"** is the bonafide original work done by me at the Department of Cardiology, Stanley Medical College and Government Stanley Hospital during the period 2011-2014 under the guidance and supervision of the Professor and Head of Department of Cardiology of Stanley Medical College and Government Stanley Hospital, **Prof. Dr. K.KANNAN, M.D., D.M., FACC**. This dissertation is submitted to THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, towards partial fulfillment of requirement for the award of D.M. Degree (Branch - II) in cardiology.

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ACKNOWLEDGEMENT

I wish to express my respect and sincere gratitude to my beloved teacher **Prof. Dr. K. KANNAN, M.D., D.M., FACC,** Professor and Head of Department of Cardiology for his valuable guidance and encouragement throughout the study.

I also wish to convey my respect and earnest gratitude to **Prof. Dr. G. GNANAVELU, M.D., D.M.,** Additional Professor of Cardiology for his valuable guidance and encouragement.

I am extremely thankful to our **Prof. Dr. G. JUSTIN PAUL M.D., D.M,** for his support and encouragement in this study.

I express my gratitude to my guide and assistant Professor **Dr. K.TAMILSELVAN** for his support and guidance**.** I also thank my assistant professors **Dr. ASHOK VICTOR, Dr. P.M.NAGESWARAN, Dr. C.ELAMARAN, Dr. R.SAMPATH KUMAR, Dr. A.ARVIND, Dr. R.ARUN, Dr. N.VISHVANATHAN and Dr. A.RUDRAPPA** for their guidance in this study.

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ABBREVIATIONS

ACS	-	Acute coronary syndrome
A	-	Late diastyolic velocity
A’	-	Late diastolic tissue velocity
AMI	-	Acute Myocardial Infarction
AWMI	-	Anterior Wall Myocardial Infarction
AV	-	Atrioventricular
BMI	-	Body Mass Index
BSA	-	Body Surface Area
CABG	-	Coronary Artery By-Pass Graft
CAD	-	Coronary Artery Disease
CAG	-	Coronary Angiogram
CHF	-	Congestive Heart Failure
CHB	-	complete heart block
CSA	-	chronic stable angina

DVD - Double Vessel Disease

EA - Effort angina

E - Early diastolic velocity

E’ - Early diastolic tissue velocity

E/E’- Ratio of early diastolic velocity and early diastolic tissue velocity

E’/A’ – Ratio of early diastolic tissue velocity and late diastolic tissue velocity

IR - Isovolumic relaxation phase

IWMI - Inferior Wall Myocardial Infarction

LAD - Left anterior descending artery

LCA - Left circumflex artery

LV - left ventricle

LVEF - Left Ventricular Ejection Fraction

MI - Myocardial Infarction

MR - Mitral Regurgitation

RCA - Right Coronary Artery

SD - Standard Deviation

SVD - Single Vessel Disease

TDI - Tissue Doppler echocardiography

TVD - Triple Vessel Disease

WMA - wall motion abnormality

INTRODUCTION

INTRODUCTION

Coronary artery disease (CAD) is one of the leading cause of morbidity and mortality in the world and has nearing its epidemic proportions. Coronary artery disease causes 9.4 percent of total deaths (25 lakhs) in under developed countries and 16.3 percent (13 lakhs) of all deaths in developed countries[1]. The world health organisation (WHO) has calculated the year of 2002 alone, 12.6 percent of deaths in the world were because of CAD[2]. The proportion of CAD is expected to increase as it is disease of aging and the world population getting older.

The India has similar scenario, Indian studies has revealed that cardiovascular diseases (CVD) cause about 40% of deaths in the urban areas and 30% of deaths in rural areas in india[3]. Prevalence of cardio vascular disease in the adult population has multiplied in urban areas from around 2% in early 1960's to 6.5% in late 1970's, 7% during the year 1980, to close 10 % in 1990 and to a critical 10.5% in the year 2000, the same time in rural areas, it is increased to a smaller extent from about 2% during 1970, to 2.5% in late 1980's , and to calculated 4% in the 1990, at last the prevalence has reached 4.5% in 2000.

So prevention of cardiovascular diseases among people is more important, if cardiovascular disease occurs the earlier detection and treatment for the prevention of complication and death. Moreover

identification of risk factors and prevention of CAD is more important than treatment itself. Early detection of CAD among people with or without symptoms is main task to reduce morbidity and mortality. There are various invasive and non invasive methods to detect CAD among people with symptoms. Always invasive methods have it own advantage and disadvantages, so non invasive tests are low cost modalities of CAD detection, and are need of the hour. Of these non invasive modalities various methods used like ECG, ECHO, CT, MRI and nuclear imaging. Many non invasive methods are used for detection of CAD. Exercise stress testing like treadmill test, stress echocardiography and stress SPECT is routinely used for the non invasive assessment of coronary artery disease and is considered a safe procedure.

Diastolic stress test mainly used to diagnose elevated filling pressure in patients with exertional dyspnoea associated with normal filling pressure at rest. The elevated filling pressure during exercise reflects cardiac cause of dyspnoea, this can be measured by early mitral velocity (E) and early mitral tissue velocity (E'). This idea extrapolated in patients with chest pain with normal LV function to identify myocardial ischemia which increases LV filling pressure.

Based on the concept diastolic abnormalities occur earlier than symptoms, electrocardiographic changes and systolic dysfunction during

myocardial ischemia. Diastolic stress test should identify ischemia earlier than other type of stress test methods[4.] My study is looking into these questions and answers.

AIM OF THE STUDY

AIM OF STUDY

1. To calculate tissue Doppler velocity parameter in normal and coronary artery disease patients
2. To measure changes in TDI parameters immediately after stress
3. To identify changes in E/E' during normal and after stress
4. Changes in E/E' can detect coronary artery disease and its severity

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Since introduction of exercise echocardiography more than thirty years ago[5], a significant progress has been made to use it to detect coronary artery disease. Stress echocardiography commonly used to detect myocardial ischemia by identification of wall motion abnormalities during stress. However stress echocardiography is done by using various methods like pharmacological agents and exercise which detects wall motion abnormalities chiefly systolic changes. So detection of diastolic changes during stress was not possible initial days of echocardiography. Detection of diastolic changes during stress possible and pressure changes estimated invasively. These diastolic changes can be measured non invasively by Doppler echocardiography mainly tissue Doppler echocardiography. The non invasive measurement of exercise induced diastolic changes demonstrated by Ha et al[6] in 2005. They designed echocardiographic stress test to detect diastolic changes, which was named "DIASTOLIC STRESS TEST".

The diastolic stress test using echocardiogram was demonstrated to detect changes in LV filling and LV diastolic pressure during stress non invasively[7]. They combined supine bicycle exercise and tissue Doppler echocardiography to do diastolic stress test.

Diastolic stress echocardiography performed by measuring diastolic myocardial tissue velocity at rest followed by during exercise, which detected changes in diastolic parameters. During diastolic stress test traditional transmitral Doppler and tissue Doppler parameters like E, A, DT, E/A, S', E' and A' were measured. LV filling pressure reliably estimated using mitral inflow early diastolic velocity (E) and early diastolic tissue velocity (E'). Increase in left ventricular filling pressure occurs in patients with diastolic dysfunction which can be estimated by ratio of early mitral diastolic velocity and early mitral tissue Doppler velocity (E/E').

The exercise induced diastolic dysfunction causes increase in LV filling pressure which can be measured by ratio of early mitral diastolic velocity (E) and early mitral tissue Doppler velocity (E'). The non invasive measurement of left ventricular filling pressure by E/E' ratio is well correlated with invasive measurements by various authors and in various studies[8]. This ratio also used to identify subjects with elevated LVEDP during exercise and lower exercise capacity[9]. Initially the diastolic stress echocardiography was used to evaluate patients with exertion dyspnoea and dyspnoea of unknown origin. It also used to differentiate the cause of dyspnoea from cardiac or non cardiac origin. Ha et al applied this diastolic stress echocardiography to patients with exertion dyspnoea who

had no evidence of increased left ventricular filling pressure at rest. Their study show 36% patients had increase in left ventricular filling pressure on the basis of E/E' ratio during stress. Diastolic stress test also differentiates patients with organic heart disease who have normal hemodynamic and asymptomatic during resting state and symptoms precipitated only during exertion. The patients with exertion dyspnoea which is not explained by normal cardiac performance at rest, but they can have change in LV diastolic parameters during exercise compared with those who don't have symptom of exertion dyspnoea despite same LV systolic and diastolic function during rest.

Diastolic stress echocardiography:

Patients with diastolic dysfunction have abnormalities of relaxation that prevents augmentation of relaxation when heart rate increases with exercise, thereby increase LV filling pressure and LA pressure. This technique can be used to detect increase in left ventricular filling pressure during exercise in patients with exertion dyspnoea and normal resting LV systolic and diastolic function. Tissue Doppler imaging is one of the methods to evaluate diastolic function or myocardial relaxation by measuring mitral annular velocity in diastole.

Diastolic functional reserve:

Diastolic functional reserve defined as capacity of the ventricle to augment or increase diastolic filling needed for increase in demand of cardiac output without increase in ventricular filling pressure.

Uses of diastolic stress test:

1. Differentiate and gives diagnostic finding that useful in management of patients with dyspnoea of unknown aetiology
2. To detect coronary artery disease
3. To determine exercise capacity

Mechanism of diastolic dysfunction during ischemia

Myocardial relaxation is an active process and energy demanding process therefore it vulnerable to ischemia[10, 11]. So it has been shown that recurrent myocardial ischemia can induce structural change of the myocardium which leads to impaired early diastolic motion[12]. These changes in diastolic wall motion can be detected by Tissue Doppler imaging (TDI) at rest in ischemic regions[13]. TDI can quantify regional myocardial function. In experimental studies showed myocardial velocity falls progressively 15 secs after onset of ischemia[14]. The measurement of myocardial velocity has been proposed an objective marker of myocardial function during stress. Regional stunning due to myocardial ischemia can

be diagnosed by tissue Doppler measurements. The myocardial ischemia can also be detected by measurement of reduced transmyocardial velocity. These regional diastolic dysfunction can be detected and measured by TDI, so TDI parameters like systolic velocity (S'), early diastolic velocity (E'), and late diastolic velocity (A') can reflect changes during ischemia. Changes documented during ischemia are reduced and delayed peak systolic and diastolic velocities, reduced myocardial velocity gradients and diastolic dysfunction, which demonstrated in various studies. In post treadmill exercise echocardiography also identifies diastolic dysfunction immediately after cessation of exercise, Because diastolic dysfunction may persist after recovery of normal systolic function, after short time of coronary occlusion by balloon during coronary angioplasty[15].

LV walls like anterior, IVS, inferior, posterior and lateral are divided into basal, mid and apical segments. These segments have individual velocities, which can vary segments to segment. Some studies measured basal and mid segments[16] and some studies measured only basal segments [17]. But during ischemia velocity and gradient from base to apex is altered or reduced. And LV apex relatively an immobile structure, so measurement of velocity in basal segments ideal to detect ischemia induced velocity changes.

In a study by Hoffman [17] et showed the global early diastolic tissue velocity E' was reduced in one and two vessel disease and normal in three vessel disease. Global late diastolic tissue velocity A' was increased in one vessel disease and not increased in two and three vessel disease. The E'/A' reduced in one vessel disease. Regional systolic velocity S' was lower in ischemic segments of the vessel supplied and S' significantly lower in three vessel disease.

The TDI parameters described by Hoffman et al given as follows

TDI parameters	NON- CAD	CAD
S'	6.06+- 0.89	5.58+- 0.96
E'	6.78+- 1.46	6.31+-1.65
A'	7.16+-1.32	7.16+-1.53
E/E'	10.4+-2.66	11.6+-3.99

Garcia et al[18]showed regional myocardial ischemia causes reduction of early diastolic tissue E' velocity in animal models, following this demonstrations pouleur et al[19] showed E' velocity reduced during myocardial ischemia in humans. The significant reduction of early diastolic velocity E' in ischemic region demonstrated in patients with one vessel disease, two vessel disease and three vessel disease [18]. The reduction in early diastolic velocity E' might be caused by increased LV filling

pressure as myocardial ischemia worsens. In patients with one vessel disease the early diastolic velocity E' of the segment supplied by stenotic artery decrease and late diastolic velocity A' increases resulting in significant reduction of E'/A'. As severity of CAD increases and involving more than one vessel this late compensation was lost and decline in global diastolic and systolic function follows.

Important landmark MYDISE[16] (myocardial Doppler in stress echocardiography) study done by using pharmacological agents (dobutamine) and it showed mean systolic velocity was less in women than men and inverse relation between age and systolic velocity at peak exercise or peak stress. Peak systolic velocity at peak stress correlated with height. Patients with CAD had lower peak systolic velocity than non CAD group. Peak systolic velocity increases > 100% in healthy volunteers than 50-70% in patients with CAD. MYDISE study demonstrated peak systolic velocity at peak stress was better discriminator of disease. The average peak systolic velocity in basal anterior segment, basal lateral and basal inferior segments are 10.3cm/sec, 10.8cm/sec and 12.8 cm/sec respectively. Above these following cut of systolic velocity(S') in a myocardial segment clearly discriminates without coronary artery disease.

The average peak cut off systolic velocity of myocardial segments with CAD in MYDISE study

Myocardial segments	Systolic velocity (S') cm/sec (avg)
Basal anterior	10.3
Basal lateral	10.8
Basal inferior	12.8

The MYDISE study showed sensitivity and specificity of individual coronary artery stenosis by diastolic stress echocardiography with above cut of systolic velocity as follows

ARTERY	SENSITIVITY	SPECIFICITY
LAD	80%	80%
LCX	91%	80%
RCA	93%	82%

A diastolic stress test study by tsougos et al[20] demonstrated positive treadmill exercise test was observed in 68% patient and wall motion abnormality observed in 76% of patients with CAD group. The E/E' ratio is similar in septal and lateral wall in resting stage. This study showed CAD group had an increase of E/E' average compared with

the non-CAD group: 56 of 72 patients (78%) versus 10 of 42 patients (24%) (P <0.001). This study obstructive CAD group had increase of E/E' average immediately after exercise, the sensitivity of the method is 77.8%, the specificity 76.2%, and the accuracy 77.2%. The patients with an exercise-induced increase of E/E' average, 85% had CAD and 15% no CAD. But the patients with no exercise-induced increase of the ratio 33% had CAD, and 67% had no CAD. The treadmill test duration was 6.9±2.1min in patients with exercise-induced increase of E/E' average compared with 6.8±1.9min in patients without increase of the ratio.

Zagatina et al[21] demonstrated application of TDI in exercise echocardiography to detect coronary artery disease, they concluded that TDI gives highly reproducibility and minimal variation in inter observer variability. They studied 123 patients with TDI of systolic and diastolic function during stress echocardiography. Patients with negative treadmill test and normal coronaries compared to positive treadmill test and abnormal coronaries had higher exercise capacity, peak systolic BP and peak HR. In this study subjects without CAD had higher exercise capacity (127.9 W) compared to with CAD (93.9W). The peak HR and sysytolic BP during stress was higher in patients without CAD (131.7 beats/min) (177.7 mmhg) than with CAD (114.9 beats/min) (162 mmhg).

Systolic tissue Doppler velocity is better predictor of CAD than diastolic tissue Doppler velocity after exercise. The mid septal wall maximum systolic velocity post-stress (5.68 ±1.62 cm/s) in CAD compared to non CAD (8.02 ± 1.72) and P value <0.001. the basal anterior wall maximum systolic velocity post-stress (6.42 ± 2.26cm/s) in CAD compared to non CAD (11.8 ± 3.58) and P value of < 0.005. The mid lateral wall mean systolic velocity post stress (3.01 ± 1.25 cm/s) in CAD compared to non CAD (5.34 ± 1.81) and P value of < 0.005. the early diastolic tissue velocity (E') post-stress (10.9 ± 2.92 cm/s) in CAD compared to non CAD (14.0±5.10) and P value of <0.05. They showed CAD without LAD disease had reduced systolic and diastolic velocity compared to normal subjects; however involvement of LAD significantly reduced all above velocities. Diastolic tissue Doppler velocity predicts CAD earlier than systolic tissue Doppler velocity. It showed sensitivity, specificity and accuracy to detection stenosis in LAD as 96.1%, 62.4% and 86.2% respectively. The sensitivity, specificity and accuracy for the detection LCX disease was 87.7%, 66% and 78.3% respectively. However it doesn't give any criteria to diagnose RCA stenosis.

Williams et al[22] investigated 26 patients for systolic velocity, diastolic velocity, strain rate and strain in normal coronaries and CAD without infarction. They followed treadmill test followed by

immediate echocardiography to measure tissue velocity. The measurements at rest and peak exercise and post TMT for one hour with intervals. Tissue velocity measurements were taken at basal segments. The mean exercise time was 20% lower in CAD group than non CAD group.

Peak systolic velocity increases by 30% in CAD group than 92% in non CAD group. The small increase in systolic velocity of ischemic myocardium is due to tethering effect of adjacent normal myocardium[23]. The diastolic velocity E' and A' doesn't change in CAD group during peak stress but both were increased in non CAD group [24, 25]. But diastolic strain rate decreases by 24% in early diastole and 28% during atrial contraction.

Bolognesi et al[26] evaluated patients with CAD with normal EF for invasive hemodynamic measurements combined with tissue Doppler imaging, and found suction like effect during early diastolic filling significantly reduced in early stages of CAD. It showed peak E velocity (cm/s) without CAD 75.0 ± 13.2 compared to with CAD 55.2 ± 12 P value <.01 significantly reduced in contrary to latest studies. The peak A velocity (cm/s) 59.0 ± 4.5; 58.15 ± 14.8) was same in patients with or without CAD. However the peak systolic tissue velocity (S') and diastolic tissue velocity (E', A') were significantly reduced in patients with CAD than normal group. The E' velocity was lower and E' acceleration time

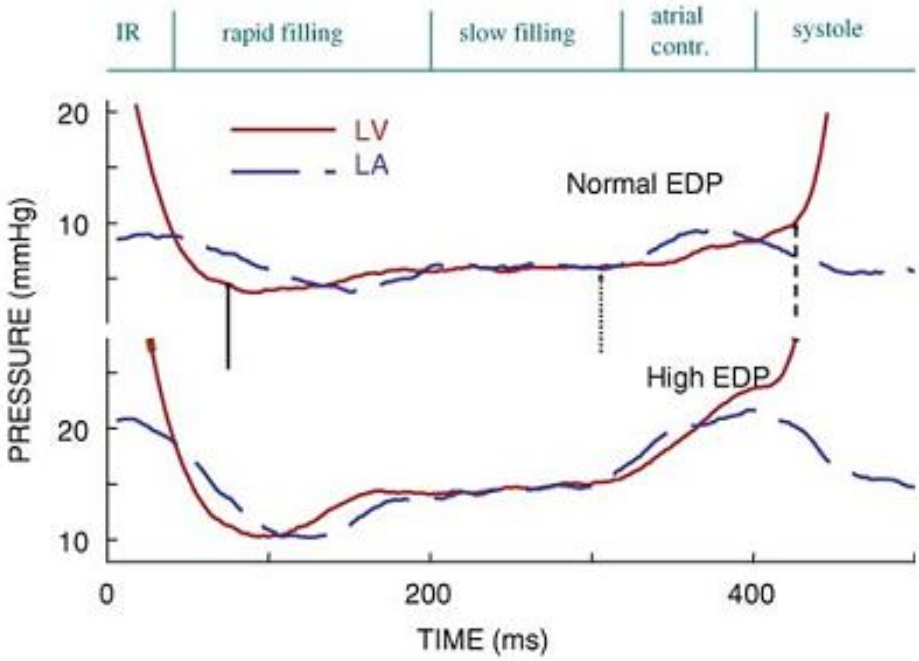
longer than non CAD group which explained by weakness of elastic properties of LV and reduced early diastolic recoil of LV due to myocardial ischemia.

Dounis et al[27] studied type 2 DM and diabetic CAD patients with normal EF by tissue Doppler imaging for systolic and diastolic myocardial velocity. They showed decreased early diastolic tissue velocity in diabetics than control subjects (8.8±1.8 vs 10.1±1.7 cm/s; p=0.02). E' was inversely correlated with age, HbA1c and pulse pressure. Moreover the reduction of early diastolic tissue velocity in diabetics was similarly to diabetic CAD. They concluded that impaired diastolic function in diabetics similar to diabetic CAD. Bruch C et al [28] concluded that TDI useful to detect CAD using diastolic parameters in patients with normal systolic function.

Diastole physiology:

The cardiac cycle has systolic ejection period and diastolic filling period. The systolic and diastolic function must increase with increase in demand such as exercise and others. The ventricle diastolic function has to increase with demand without increase in LA pressure. Left ventricular diastole starts with aortic valve closure and it includes following phases of diastole

1. Isovolumic relaxationIR)
2. Rapid filling
3. Slow filling
4. Atrial contraction(AC)



The above diagram shows LV diastole during normal filling pressure and elevated filling pressure (high EDP)

Both ventricles are initially filled by the pressure gradient and finally by the respective atrial contraction. Isovolumetric relaxation phase starts with aortic valve closure until mitral valve opening during which ventricular pressure reduces to lower levels without significant changes of both ventricular volumes. During isovolumic

relaxation phase ventricular pressure falls from peak that attained at the end of cardiac systole. This IR phase is energy dependent and may be more vulnerable to myocardial ischemia. During rapid filling phase majority of the ventricular filling occurs which is also energy dependent but partially. When both ventricular pressures drops lower than atrial pressure, AV valves opens and the blood flows from atrium to the ventricles. As rapid filling wave progresses increase in ventricular volume is affected by LV myocardial characteristics especially stiffness.

In slow filling phase as both ventricles go on to fill with blood, the intraventricular pressure starts going up as the ventricles became less compliant. So the decrease in pressure gradient across the atrioventricular valve causes decrease in ventricular filling. The slow filling phase is also affected by the above myocardial characteristics especially stiffness. Myocardial passive stiffness can be increased by fibrosis resulting from many factors such as myocardial ischemia, myocardial infarction, infiltrating process like amyloidosis, myocyte hypertrophy and valvular heart disease. About 85-90% of the both ventricular filling takes place at the end of the phase. The atrial contraction phase contributes to about 10-15% of ventricular filling however in certain diseased states and older age it may even contributes to about 30-40% (due to diminished early relaxation).

Normal diastolic filling pattern:

In normal young adults, LV relaxation is an active process and maximum LV filling occurs during early diastole. Thus echocardiography characteristics as follows

1. E/A ratio > 1.5
2. Decceleration time (DT)- 160-240 ms
3. Septal E' > 10cm/sec
4. Lateral E' >15cm/sec
5. E/E' < 8
6. Vp > 50 cm/sec

In normal myocardial relaxation, mitral inflow early diastolic velocity E is greater than late diastolic velocity A, so E/A usually more than 1.5. which reflects in mitral annular longitudinal velocity pattern E' is always greater than A'. The lateral annulus velocity (normal E'>15cm/sec) is usually higher than septal annular velocity (normal E' > 10cm/sec).so early mitral annulus velocity E′ always increases with exercise in normal young adults. So the E/E′ is same at rest and during exercise (usually <8). In older age there is gradual decline in rate of myocardial relaxation. So there is slowing of LV pressure decline and slow myocardial relaxation mimics grade 1 diastolic dysfunction. So at the age of 65 E velocity equals A velocity, and in age greater than 70 years

the E/A ratio reverses that is < 1.0. In older age group the reversal of E′/A′ occur 10 to 15 years earlier than E/A.

Normal diastolic function and aging:

Normal aging was shown to affect diastolic ventricular relaxation and diastolic filling in healthy adults. Factors that slow LV relaxation in most normal individuals are increase in systolic blood pressure and LV mass, which leads to changes in LV diastolic parameters. Most of elderly subjects will have equal reversal of peak E and peak A velocity at the age of 70. In individuals without elevation of blood pressure and LV mass still can have normal E and A pattern of diastolic function. TDI velocity also age dependent, there was no difference in systolic velocity but early diastolic tissue velocity E' and late diastolic tissue velocity A' reduced in elderly subjects [29, 30.]

Factors affecting LV diastolic function:

External factors:

Pericardial factors like retriction and constriction

Ventricular factors

Extrinsic factors like fluid, mass and others

Internal factors:

LV characteristics like compliance and stiffness

LV wall thickness due to muscle, fibrosis, amyloid and others

Diastolic rigor, tone, contracture

LV recoil like suction effect

Viscoelastic properties of LV like creep

Assessment of diastolic function:

Echocardiography evaluation of diastolic function is an integral part of cardiac assessment. There are various technique and parameters recommended to evaluate diastolic function and validation of these parameters done with invasive measurements. The TDI assessment of diastolic function is less load dependent than by Doppler transmitral velocity which is preload dependent. The methods for evaluation of diastolic function are 2D echo, Doppler echo, TDI, colour M mode, mitral and pulmonary artery flow velocity.

Doppler echocardiography:

Doppler echocardiography is used to measure blood velocity using RBC's as targets. Doppler echocardiography measures low amplitude, high velocity (10-150cm/sec) signals.

Mitral flow velocity:

The mitral flow velocities were recorded with pulsed wave Doppler with the sample volume placed at the tip of the mitral valve from the apical four-chamber view. From the mitral valve inflow velocity curve the following measurements were made: peak E-wave velocity and its DT, peak A-wave velocity, and the isovolumic relaxation time were measured from aortic valve closure to the mitral valve opening.

The transmitral velocities (E and A wave) are directly related to left atrial pressure (preload) and independently and inversely related to ventricular relaxation. So mitral inflow patterns are highly sensitive to preload and its changes. This can change dramatically as diastolic dysfunction progresses, the use of mitral valve inflow patterns to assess diastolic function remains limited.

Normal mitral inflow parameters as follows,

Mitralinflow parameters	Age group 45-49	50-54	55-59	60-64	65-69	>70
Ewave m/sec	0.7 0.5-0.9	0.6 0.5-0.9	0.7 0.5-0.9	0.7 0.5-0.9	0.6 0.4-0.8	0.6 0.4-1.0
Awave m/sec	0.5 0.3-0.7	0.5 0.4-0.8	0.6 0.4-0.9	0.6 0.4-0.9	0.7 0.4-1.0	0.8 0.5-1.1
E/A ratio	1.3 1.0-2.0	1.2 0.8-2.0	1.2 0.7-1.8	1.0 0.7-1.6	1.00 0.6-1.50	0.8 0.6-1.3
DT msec	208 180-258	217 178-266	210 183-187	222 180-282	227 188-298	242 188-320

Tissue Doppler imaging:

Tissue Doppler imaging is an ultrasonographic method to image and measure velocity of myocardial tissue with modified pulse wave Doppler echocardiography. Myocardial velocity is much lower than blood (1-2cm/sec) but higher amplitude. So the Doppler principle modified to quantify higher amplitude, lower velocity signal of myocardial tissue motion. The sample volume was placed at the junction of the LV wall with the mitral annulus of the septal and lateral myocardial segments from the four-chamber view and inferior and anterior myocardial segments

from the two-chamber view. It can also be measured in mid segments of LV wall. Peak velocities during systole (S'), early diastole (E'), and late diastole (A') were measured.

Because the apex remains relatively stationary throughout the cardiac cycle, mitral annular motion is a good surrogate measure of overall longitudinal left ventricular (LV) contraction and relaxation.[31]

Limitation of TDI:

The important limitations to Tissue Doppler imaging modality is, it measures only the vector of motion that is parallel to the direction of the ultrasound beam. In addition, TDI measures absolute tissue velocity and is unable to discriminate passive motion (related to translation or tethering) from active motion (fiber shortening or lengthening).

Systolic myocardial tissue velocity (S'):

The systolic myocardial velocity S' is above the baseline in TDI as mitral annulus moves towards apex during systole.

Normal S' velocity varies with age, sex and myocardial segments, and normal velocity of different segments as follows [32]

S wave cm/sec	*Myocardial segment*			
	Septal wall	Lateral wall	Inferior wall	Anterior wall
Basal segment	5.97 ± 1.14	6.26 ± 2.44	6.52 ± 1.31	6.44 ± 2.32
Mid segment	6.29 ± 1.89	4.48 ± 0.92	5.21 ± 2.79	5.1 ± 1.16
Apical segment	4.42 ± 2.3	4.81 ± 1.97	2.97 ± 1.14	3.8 ± 2.66

Early diastolic myocardial velocity (E'):

The early myocardial diastolic relaxation velocity measure below the baseline in TDI as mitral annulus moves away from apex. Its normal value is 12+4 cm/sec at rest and 15+5 cm/sec peak exercise. It varies with age, sex and segments as follows [32]

E' wave cm/ sec	*Myocardial segment*			
	Septal wall	Lateral wall	Inferior wall	Anterior wall
Basal segment	7.91 ± 2.16	8.54 ± 2.77	9.01 ± 2.44	8.09 ± 2.48
Mid segment	8.39 ± 2.5	6.85 ± 1.86	6.82 ± 3.16	7.22 ± 2.04
Apical segment	6.03 ± 2.95	6.74 ± 2.58	4.76 ± 1.94	4.52 ± 2.95

In normal heart without any impairment of relaxation E' increases with increase in transmural gradient, increase in preload, dobutamine infusion and exercise.

Regional myocardial dysfunction and surgery involving mitral annulus can affect mitral annulus velocity. Lateral annulus velocity is lower than medial annulus velocity in lateral wall myocardial infarction.

Late diastolic myocardial velocity (A'):

It varies with above mentioned factors and its normal value as follows [32]

A' wave cm/sec	*Myocardial segment*			
	Septal wall	Lateral wall	Inferior wall	Anterior wall
Basal segment	5.99 ± 1.73	3.77 ± 1.95	5.84 ± 2.06	3.86 ± 1.75
Mid segment	4.87 ± 2.14	4.9 ± 1.72	2.62 ± 1.84	4.78 ± 1.7
Apical segment	2.69 ± 1.93	3.77 ± 2.1	3.08 ± 1.54	1.69 ± 1.45

Mitral annulus late diastolic velocity (A') is increase during early stage of diastolic dysfunction but decreases when atrial function deteriorates.

Uses of TDI:

1. Estimation of LV filling pressure
2. Early diagnosis of genetic disease like HCM, fabry disease [33]
3. To diffentiate HCM from athlete heart [34]
4. Assessment of RV function [35]
5. Differentiation between constriction and restrictive disease [36]

Definition of diastolic dysfunction:

Diastolic dysfunction is defined as abnormalities of ventricular filling during diastole. Abnormalities in diastolic function can occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal systolic function [37]. This is a disorder of left ventricular filling, which leads to reduction of LV end diastolic volume and cardiac output, during rest and exercise. Inability of left ventricle to fill without increase LV end diastolic pressure and mean LA pressure.

Various pattern and grades of diastolic dysfunction described as follows,

Grade 1 diastolic dysfunction:

This is a mild form of left ventricular diastolic dysfunction and is an early abnormality of diastolic function. The other names are given to grade 1 LVDD like delayed relaxation pattern, impaired relaxation pattern, reversed E/A ratio. In subjects with Grade 1 LVDD

filling pressures are normal. They have E/A ratio < 1. Deceleration time is greater than 240 milliseconds.

Common cardiac conditions lead to this type of LVDD is LVH, myocardial ischemia, myocardial infarction, hypertrophic cardiomyopathy and diabetes mellitus. These patients can have increase in the IVRT. Various ECHO abnormalities noted in patients with DD are septal E' less than 7 cm, mitral flow propagation velocity less than 50 cm/sec and E/E' greater than 8.

Subgroups of patients with Grade I LVDD have a unique echo abnormality. They have E/A ratio less than 1 but E/E' greater than 15 indicating increase in filling pressure which is not usually seen in patients with grade 1 LVDD. This abnormality is designated as grade 1a LVDD.

Grade 2 LV diastolic dysfunction:

This grade refers to moderate form of LVDD. This form of diastolic dysfunction is also called pseudo normalization of LVDD. This echocardiographic pattern resembles the normal diastolic filling pattern such as E/A ratio between 1 to 1.5 and DT ranging 160 to 200 milliseconds. The following points easily differentiate the pseudo normalization of diastolic dysfunction from normal diastolic filling pattern.

1. Presence of mid diastolic flow
2. While valsalva manoeuvre the underlying impaired relaxation pattern is unmasked, whereby E/A ratio decreases to > 0.5.
3. During valsalva manoeuvre if A velocity increases – it indicates pseudo normalization of diastolic dysfunction.
4. Prolongation of pulmonary vein atrial flow reversal and shortening of mitral A duration which exceeds mitral A duration indicates the pseudo normalization of LVDD.
5. E' less than 7

Grade 3 and 4 diastolic dysfunction:

These are the severe forms of LV diastolic dysfunction. The grade 3 LV diastolic dysfunction is a reversible form of diastolic dysfunction. The Grade 4 LV diastolic dysfunction is a irreversible form of diastolic dysfunction. These are also called as restrictive filling pattern or restrictive physiology. There are various cardiac abnormalities which can cause this severe type of restrictive diastolic dysfunction pattern are constrictive pericarditis, severe coronary artery disease, decompensated systolic heart failure, advanced restrictive cardiomyopathy and acute severe aortic regurgitation.

The echocardiographic abnormalities that are noted in grade 3 and 4 LVDD or severe diastolic dysfunctions are:

1. Increased early transmitral velocity ‘E’ velocity
2. Decreased late velocity ‘A’ (markedly reduced than ‘E’)
3. E/A ratio greater than 2
4. Decreased DT (less than 160 milli seconds)
5. IVRT (less than 70 milli seconds)
6. Pulmonary vein systolic forward flow velocity reduced
7. Early mitral annulus velocity (E’ < 7cm/sec) is decreased
8. E/E’ ratio is greater than 15.
9. Valsalva manoeuvre reverses grade 3 diastolic dysfunction (reversible form of severe diastolic dysfunction) to grade 1 to 2 pattern. But the grade 4 diastolic dysfunction cannot be reversed by Valsalva manoeuvre because LV filling pressure markedly elevated.

Clinical applications of diastolic function assessment

1. Echocardiographic assessment of diastolic function in patients with dyspnoea due to diastolic heart failure (DHF) or Heart failure with normal EF (HFnEF).

2. Echocardigraphic assessment of diastolic dysfunction to differentiate dyspnoea from cardiac or non cardiac aetiology.

3. To diagnose early changes of myocardial ischemia in the form of diastolic dysfunction in patients with early stages of ACS**.**

4. To evaluate LV filling pressure due to various aetiology.

5. To evaluate cardiac function in cardiomyopathy,

6. For prognostic assessment.

OPD evaluation of Chest pain:

Acute chest pain is one of the leading symptom drives patient to hospital, clinics and physician office. The diagnosis of acute coronary syndrome (ACS) is made if the patient has typical angina pain, risk factors, ECG changes and positive cardiac enzymes. Only 15-25% of patients present with acute chest pain diagnosed to have ACS[38], remaining percentage of patients either non cardiac life threatening condition or a non cardiac non life threatening conditions or ACS without evidence of ACS. Patients presented with chest pain to hospital were discharged without ACS can actually have ACS in 2%. There are recent advances in early and accurate detection of ACS by biomarkers , stress testing, radionuclide scanning and CT angiogram. Still ACS missed in patients with chest pain due to limitation of various testing modalities. To overcome these limitations various diagnostic modalities developed to detect myocardial ischemia in various stages of ischemic cascade.

Ischemic cascade:

We should know what happens to myocardium during ischemia and how it produces clinical manifestations. During the initial stages of coronary occlusion there is demand supply mismatch following that there is changes in biochemical milieu. Subsequently diastolic dysfunction develops as time progress wall motion abnormalities prone to occur. After the development of systolic dysfunction electrocardiographic changes manifest as a marker. Chest pain is the last manifestation to appear in myocardial ischemic cascade [39.]

After restoration of blood flow to the ischemic segments clinical manifestation first to disappear and other systolic and diastolic abnormalities disappear subsequently within hours to days according to severity and duration of coronary occlusion. Alam et al [40] studied 12 subjects undergoing PTCA for chages during coronary occlusion by balloon angioplasty. Which showed reduced endocardial velocities, thinning and systolic dysfunction. These changes occur 15-20 secs after balloon occlusion and normalised within 15-20 secs after deflation of balloon. Myocardial ischemia causes diastolic dysfuntion by which it significantly increases LV end diastolic pressure and depression of EF without concurrent chestpain [41]

Non invasive methods of CAD detection:

Exercise physiology:

Exercise testing is one of the important non invasive test modality evaluate cardiopulmonary status for stress. Exercise gives most physiologic way of stress and it increases cardiac output by six times and metabolic rate up to 20 times. Other modalities of non invasive testing can be combined with exercise test, so stress echocardiography, stress MPI and other stress modalities possible. These stress testing modalities gives functional, diagnostic and prognostic information. With exercise, in normal supine persons, the elevation of cardiac output results almost entirely from an increase in heart rate, with little augmentation of stroke volume. In the upright posture, the increase in cardiac output in normal individuals results from a combination of elevations in stroke volume and heart rate.

Exercise capacity measured in standardised measurement of metabolic equivalents (METS), calculation of METS by following formula by treadmill exercise and bicycle ergometry.

Vo2 ml/min/kg = (2.68x mph) x (0.1 + (gradex1.8))+3.5

This oxygen consumption (Vo2) can be divided by 3.5 to metabolic equivalents. Cycle ergometry can be converted into treadmill METS by the

following formula Oxygen extraction in the coronary circulation is almost maximal at rest. The only significant mechanism available to the heart to increase oxygen consumption is to increase perfusion, and there is a direct linear relationship between Mo_2 and coronary blood flow in normal individuals. The principal mechanism for increasing coronary blood flow during exercise is to decrease resistance at the coronary arteriolar level. In patients with progressive atherosclerotic narrowing of the epicardial vessels, an ischemic threshold occurs, and exercise beyond this threshold can produce abnormalities in diastolic and systolic ventricular function, electrocardiographic changes, and chest pain.

Treadmill METS = 0.98(Cycle ergometry METS) + 1.85

Stress ECG:

It is one of the several, frequently done non invasive techniques to diagnose myocardial ischemia in patients with known or suspected coronary artery disease. It measures various parameters during test. Other than ST segment changes, it also gives information about blood pressure, heart rate, exercise capacity, heart rate recovery, chest discomfort and others. Stress ECG always low cost and safe procedure but others like stress echo and stress SPECT are costly and need for pharmacologic agents and radioactive material. However all these non invasive methods have inherent limitations. Stress ECG has sensitivity

of 27-75% in patients with single vessel disease but it increases as number of vessel increased. Patients with multivessel disease have sensitivity of 81% and specificity of 66%. For left main disease and triple vessel disease the sensitivity and specificity is around 86% and 53% respectively. So the overall sensitivity and specificity of the exercise ECG in patients with CAD is approximately 68% and 77% respectively. The prevalence of an abnormal stress ECG in middle-aged asymptomatic men and women ranges from 5-12% and 20% - 30% respectively [42]

There are various exercise test modalities available, as follows

1. Arm ergometry
2. Bicycle ergometry
3. Treadmill exercise

Exercise protocols:

There are various types of protocols available, decided according to patient clinical status

1. Bruce and modified bruce proctocol- most commonly used

   the most commonly used protocol which uses three minutes stages with grades and it steadily increases oxygen consumption. Modified protocol used in elderly population as warm up for bruce stages.

2. Balke-ware protocol
3. Cornell protocol
4. ACIP and mACIP protocol

   Uses two minute stages after first two one minute stages but it gives gradual increase in heart rate, used in established CAD
5. Weber protocol

   It uses two minutes stages with 1 METS increament and it used in limited exercise capacity like compensated congestive heart failure
6. Naughten protocol

   It also uses two minutes stages with 1 METS increment.
7. Ellested protocol
8. Mc henry protocol

Pre test probability of CAD by exercise testing can be decided according to age, sex and symptoms, these are follows

1. Very low pre test probability < 5%

2. Low pre test probability 5- 10%

3. Intermediate pre test probability 10-90%

4. High pre test probability > 90%

Stress echocardiography:

Stress echocardiography is done using exercise or pharmacologic agents to provoke ischemia. Echocardiographic images examined and stored while the patient is at rest and during (or) immediately after stress (1 to 2 minutes after exercise) are compared in same plane. The test is positive if it shows wall-motion abnormalities with stress in previously normal myocardial segments or worsens in a myocardial segment that was abnormal before stress. It is true that radionuclide perfusion imaging, stress echocardiography gives information about area and extent of ischemic myocardium.

Types of stress echocardiography

There are various forms of stress echocardiography of which few commonly used as follows

I. With exercise

1. Isometric exercise

2. Arm ergometry

3. Supine bicycle exercise

4. Immediate post treadmill exercise

II. Without exercise

1. Pharmacologic stress

a. Dobutamine

b. Dypiridamole

c. Adenosine, rarely ergonavine

III. Other stress

1. Atrial pacing

2. Oesophageal atrial pacing

3. Hyperventilation

4. Cold pressor

Immediate post treadmill echocardiography: [43]

It is not possible to do echocardiography in a subject walking upright, so exercise echo designed to do before and immediately after cessation of exercise. During treadmill exercise echo typically four views captured in digital format and analysed subsequently. The views are PLAX, PSAX, A4C, and A2C. Any of standard exercise protocol can be combined with echo. During treadmill electrodes placed in such a way that echo window available to complete the task. After getting

baseline echo images and treadmill test in standard protocol is completed with traditional endpoints. There no cool down period allowed in this protocol. Post tread mill echocardiogrphic images acquired with one to two minutes after completion of treadmill.

Supine bicycle exercise echocardiography: [44]

A 2 D echocardiography is done during rest and LV parameters measured at subject with left lateral position. Supine bicycle exercise performed by the subject to undergo stress which is multistage exercise with variable load. Patients pedalled at same speed with different work load that is 25W increment at every three minutes. During each stage and recovery of supine bicycle exercise 2D echo done and various parameters measured at various planes.

Pharmacologic stress echocardiography:

Pharmacologic and Exercise stress echocardiography is a mostly accurate physiological non-invasive technique for evaluating coronary artery disease, with high sensitivities and specificities (80 vs. 85%) [45, 46, 47]. The sensitivity for stress ECHO varies with number of coronary artery involvement and its 58% for SVD and 86% for double vessel disease finally 96% for three vessel disease. It unmasks perfusion defects in the form of wall motion abnormality. It is possible with experts, not easy for

beginners and others moreover its subjective assessment, it can vary with experts. The use of pharmacological agents like dobutamine, adenosine and dypyridamole is essential. During last decade the tissue Doppler imaging proposed as valuable alternative technique for detection of myocardial ischemia as an objective tool.

Contraindication for stress echocardiography**:**

- Stress echocardiography should not be done within 24 hours of troponin positive ACS and within seven days after STEMI.
- Life threatening arrhythmia in the recent past
- pulmonary embolism and infarction
- LVF with symptoms
- Severe fixed LVOT obstruction.
- BP greater than 220/120
- Severe form of hyperkalemia
- Acute form of myocrditis,endocarditis, pericarditis,
- Acute DVT, thrombophlebitis.
- Any form of bronchospasm, blood pressure less than 90mmHg,
- Second or third degree AV block and sick sinus syndrome without pacemaker in dobutamine stress test.

Stress SPECT:

SPECT imaging uses radioactive materials to detect myocardial ischemic territories and it has its own limitations. Its sensitivity for SVD, DVD and TVD is around 61%, 86% and 94% respectively. Exercise SPECT has Sensitivity to detect CAD 87% (range, 71% to 97%) and specificity 73% to rule out CAD. Pharmacologic stress agents combined with SPECT MPI showed sensitivity of 89% and specificity of 75%, it was similar to exercise SPECT.

CT coronary angiogram:

Cardiac CT angiography is one of method for early detection of CAD in asymptomatic individuals with low and intermediate risk for CHD. It has sensitivity of 93% and specificity of 85%. Cardiac CT angiogram one of the investigation has high negative predictive value of around 99% [48] CT coronary angiogram has high negative predictive value for CAD.

Coronary angiography is gold standard method to detect and quantify CAD in any individuals

METHODS AND MATERIALS

METHODS AND MATERIALS

Patient: This analytical pre and post cross sectional study was conducted from September 2013 to February 2014. The study population includes patients attended the cardiology department OPD Stanley medical college hospital with complaints of chest pain and they are investigated subsequently they were submitted for stress ECG.

Inclusion criteria

Patients aged from 25 to 75 years who are presented to OPD with chest pain with normal LV function without ACS.

Exclusion criteria

Who not able to walk

Atrial fibrillation,

Patients with recent MI/NSTEMI/USA

More than stage 1 hypertension

Chronic kidney disease.

Valvular heart disease

ECG presence of Q wave, with bundle branch pattern/IVCD

EF of < 45%

Procedure:

- Blood test done at OPD/on admission before CAG
- Treadmill test is performed with HUSTRO- CARIOTRACK machine using bruce and modified bruce protocol.
- Stress echocardiography is performed using a standard ultrasound system (PHILIPS HD 11 XE Philips electronics, Netherlands) with a 2-4-MHz transducer during rest, at 1st min of recovery

  Patients studied in left lateral position using Philips 11XE using 2-4 MHz baseline parameters obtained before TMT. After completion of prespecified end points, patient immediately shifted to echo table which available by the side of TMT. Wall motion analysis and mitral inflow parameter and TDI parameters measured. Apical 4 chamber and apical 2 chamber view used to measure TDI parameters in basal septal, basal lateral and basal inferior wall.

Fig.1 Baseline E, A measurement in mitral Doppler echo

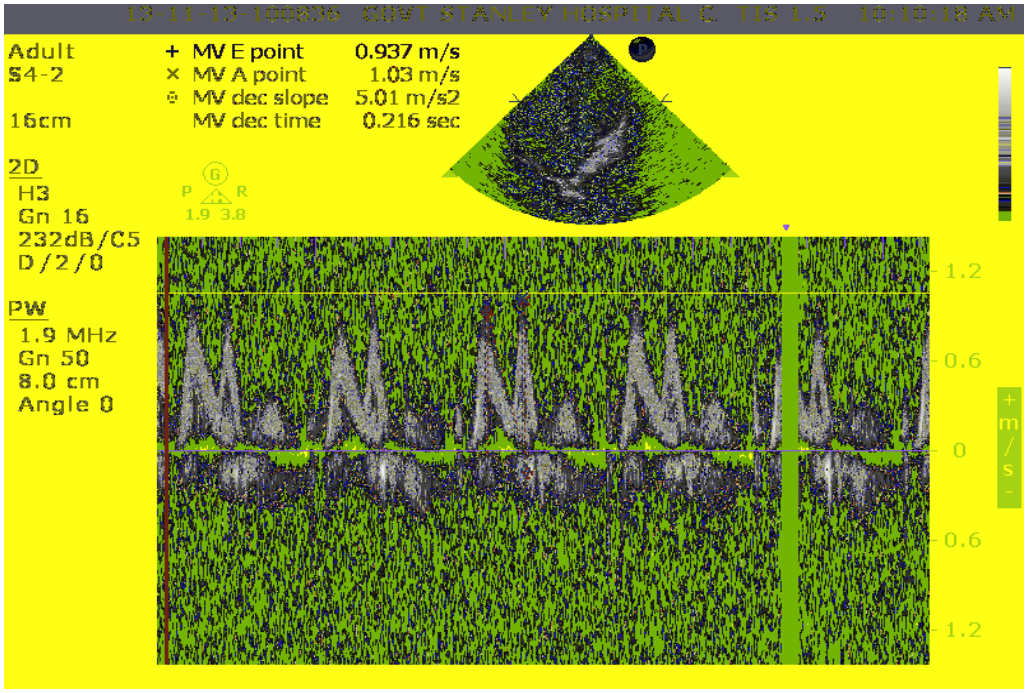


Fig.2 Post TMT stress mitral Doppler echo- reversal E/A ratio

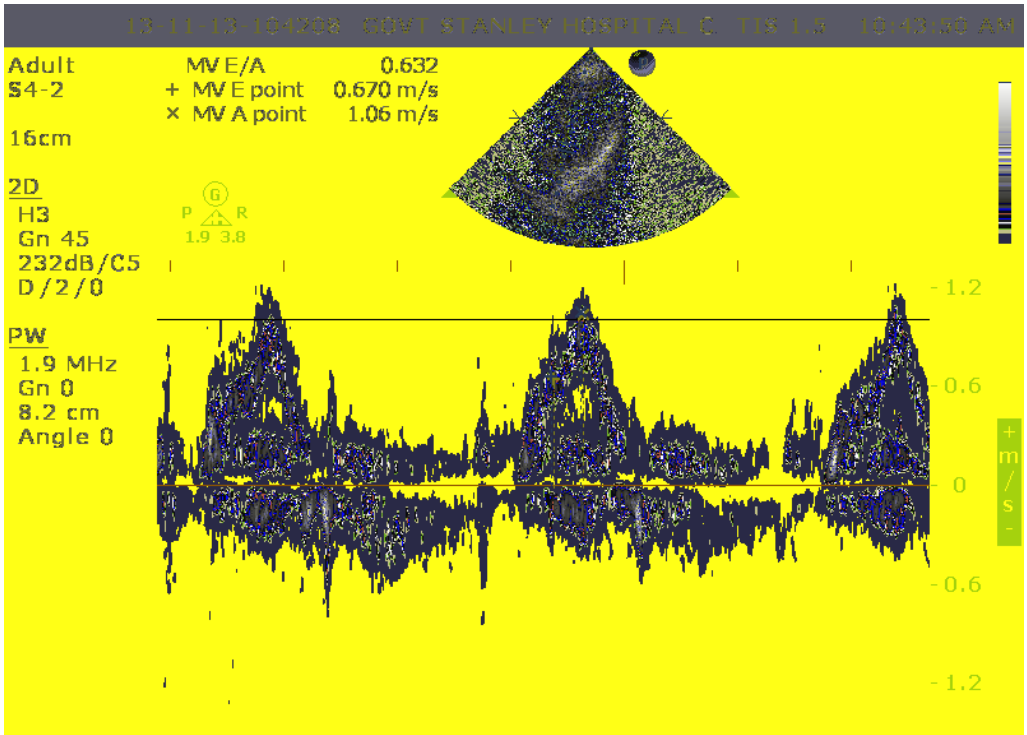


Fig.3 Baseline TDI measurements: basal anterior septum

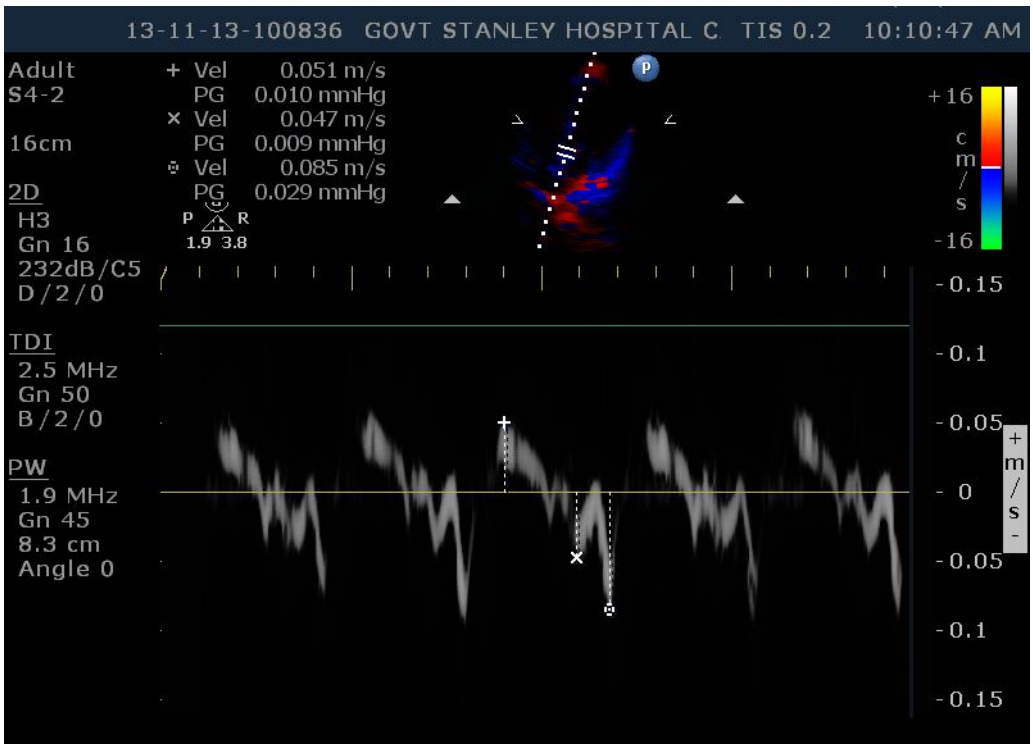


Fig. 4 Post TMT stress TDI measurements: basal anterior septum

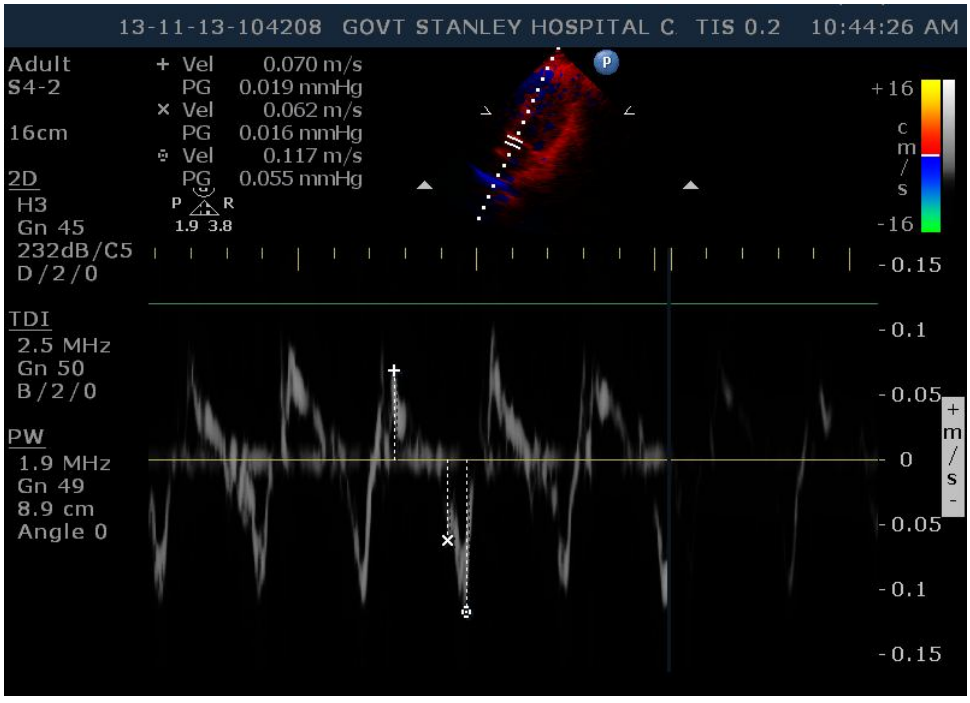


Fig.5 Baseline TDI measurement: basal lateral wall

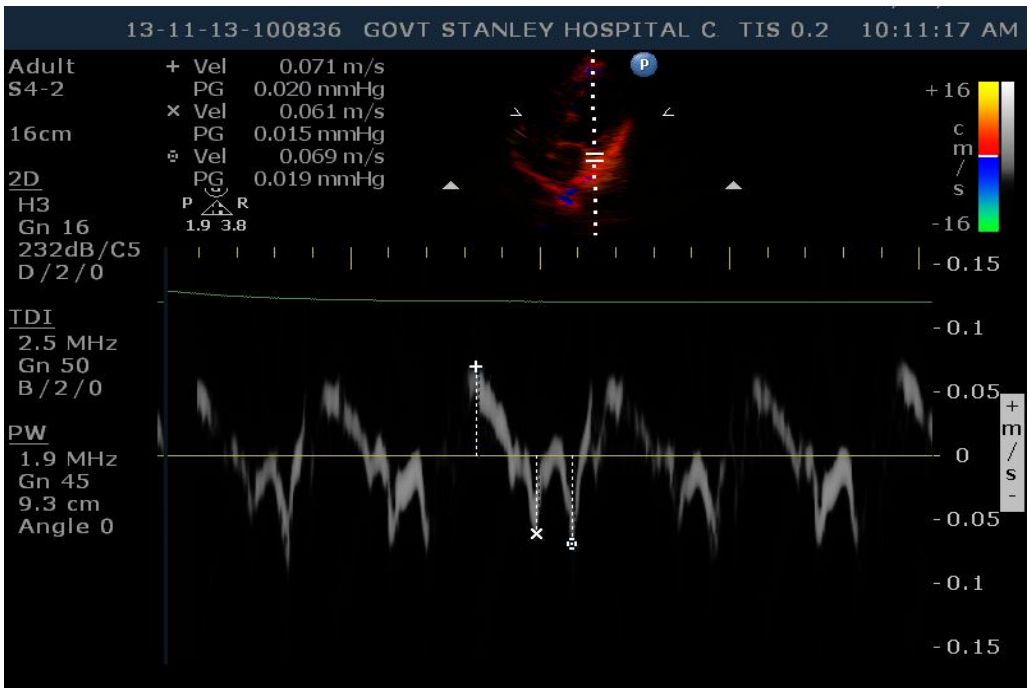
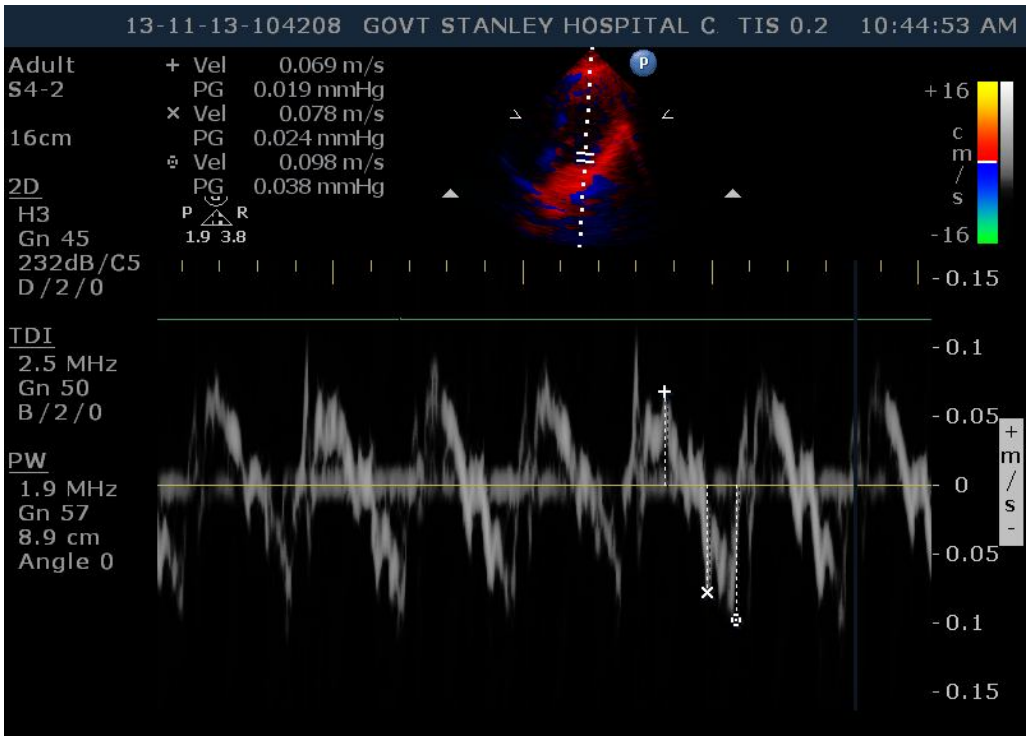
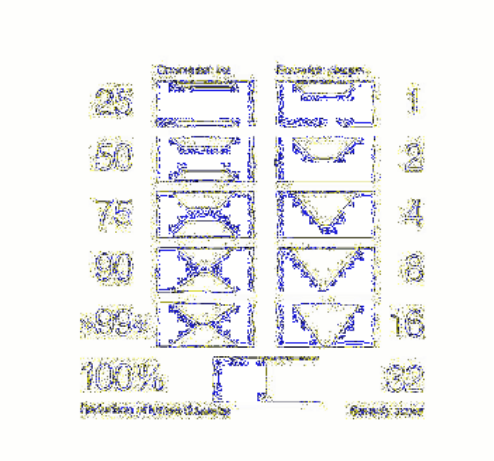


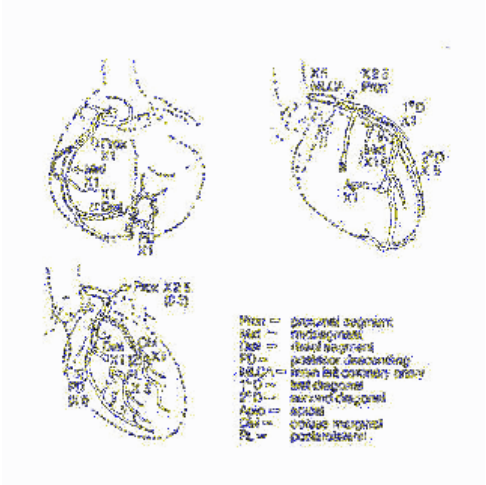
Fig.6 Post TMT stress TDI measurement: basal lateral wall



- Coronary angiography is performed with Siemens axiom altis and images recorded at a frame rate of 15/s. The patients with coronary artery lesion were identified and its severity assessed by gensini score and syntax score by experienced cardiologist

The Gensini score [49] is one method used to calculate severity in angiographic lesions and checked by a team of cardiologist. The score assigns increasing numbers to more severe luminal narrowing and also gives weight to individual segments of coronary artery affected according to vessel size and significance; segments that supply larger regions are more heavily numbered.





Syntax score[50];

It is an angiographic tool to grade complexity of CAD and ddetermines which patient amenable to which strategy, and it is semi quantitative visual score. This gives an idea about anatomical complexity anticipates procedural difficulty and outcome

- Algorithm contains 12 questions

  Q 1- DOMINANCE

  Q2- TOTAL NO OF VESSEL

  Q3 –LEISON LOCATION

  Q 4-12 LEISON CHARACTERISTICS

When the total scores calculated, it predicts MACCE and TREATMENT STRATEGY according to the score.

< 22 PCI preferable,

>22 to 32 < CABG better than PCI,

> 32 CABG definitely better and PCI with adverse events.

Figure - 7 Coronary angiogram of LCA

Statistical analysis:

The descriptive statistics was done for all data collected and suitable statistical test used for comparison. Continuous variables were analysed using unpaired t-test and Anova, categorical variables were examined with the Chi-Square Test with Yates correction. Statistical significance was taken for all correlation as p- value < 0.05. Our all data was analysed by using EpiInfo software 7.1.0.6 version; C D C, USA and Microsoft Excel 2010.

RESULTS

RESULTS: Table – 1 Age distribution in our study

Age	CAD+	%	CAD-	%
21 to 30	2	4.88	0	0
31 to 40	2	4.88	1	10
41 to 50	11	26.83	6	60
51 to 60	11	26.83	2	20
61 to 70	15	36.59	1	10
Total	41	100	10	100

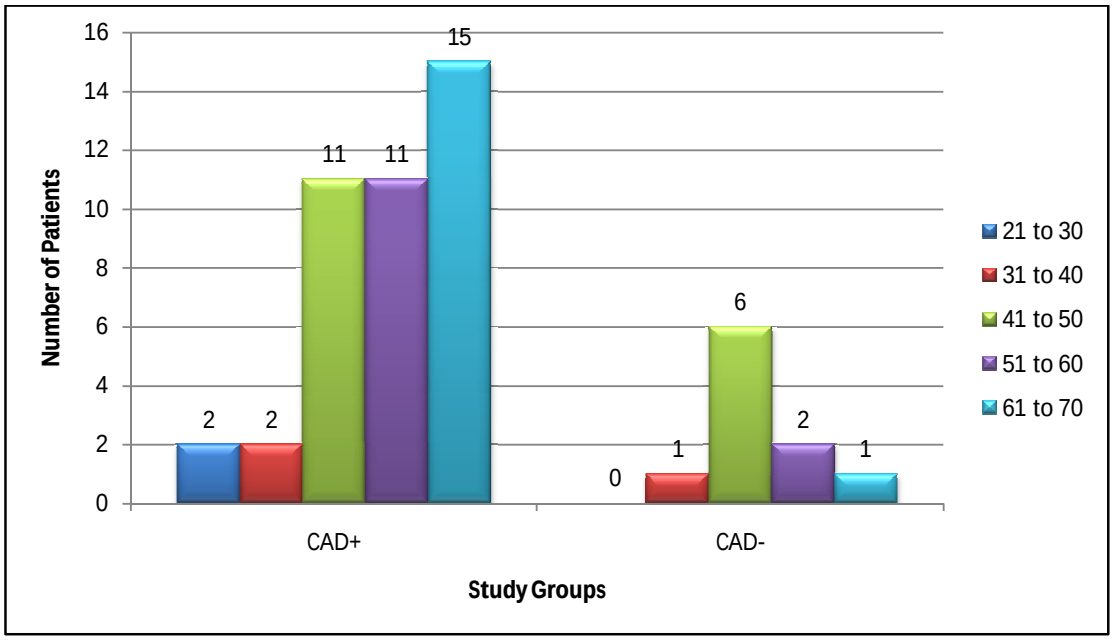
Table – 2 Average age distribution

Age	CAD+	CAD-
N	41	10
Mean	53.88	49.9
SD	10.22	7.85
P value	**0.9729**	

Table – 3 Average age in gender

Gender	CAD+	%	CAD-	%
Male	27	65.85	4	40
Female	14	34.15	6	60
Total	41	100	10	100
P value	**0.1627**			

Age distribution



Gender Distribution

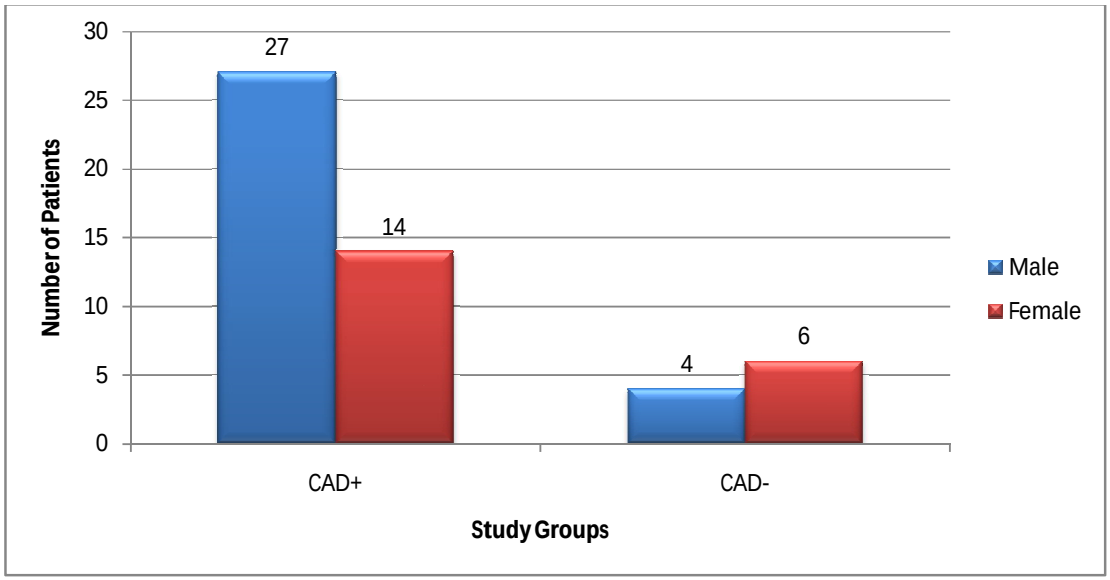


Table – 4 Smoking status comparison to CAD

Smoking Status	CAD+	%	CAD-	%
SMOKING+	18	43.90	3	30
SMOKING-	23	56.10	7	70
Total	41	100	10	100
P value	**0.4272**			

Table – 5 Hypercholestrolemia distributions in CAD patients

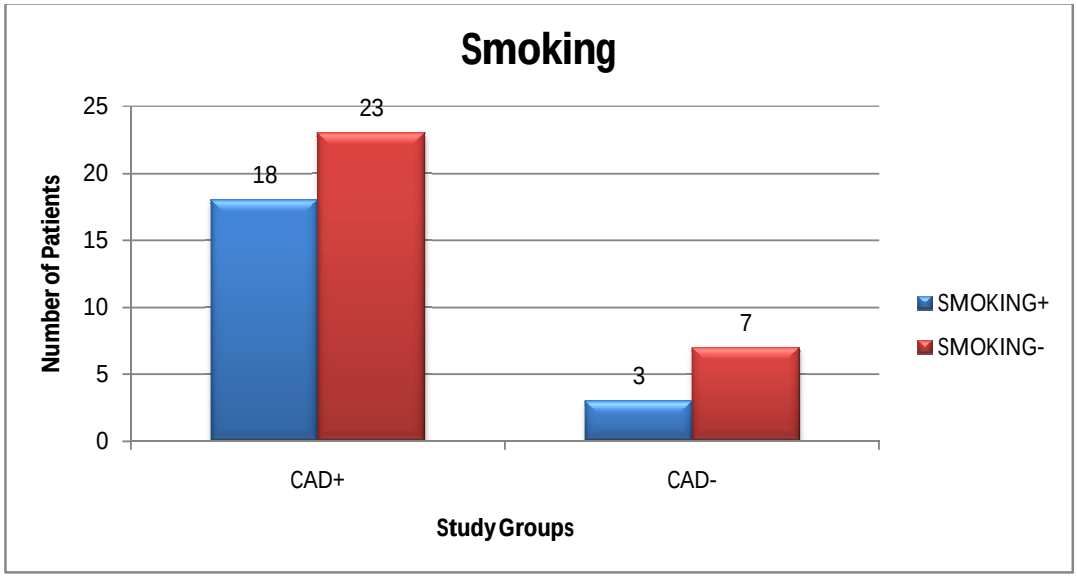
Hypercholesterolemia	CAD+	%	CAD-	%
Hypercholesterolemia	17	41.46	0	0
Normal	24	58.54	10	100
Total	41	100	10	100

Table – 6 Average total cholesterol level in CAD

Age	CAD+	CAD-
N	41	10
Mean	230.29	204.50
SD	41.26	22.96
P value	**0.01349***	

*P value is significant

Smoking status:



Hypercholestrolemia:

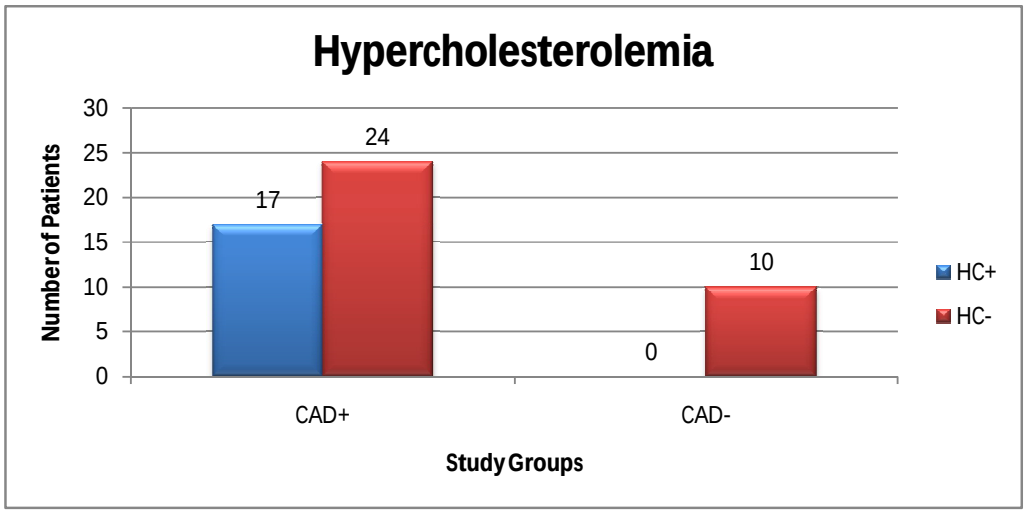


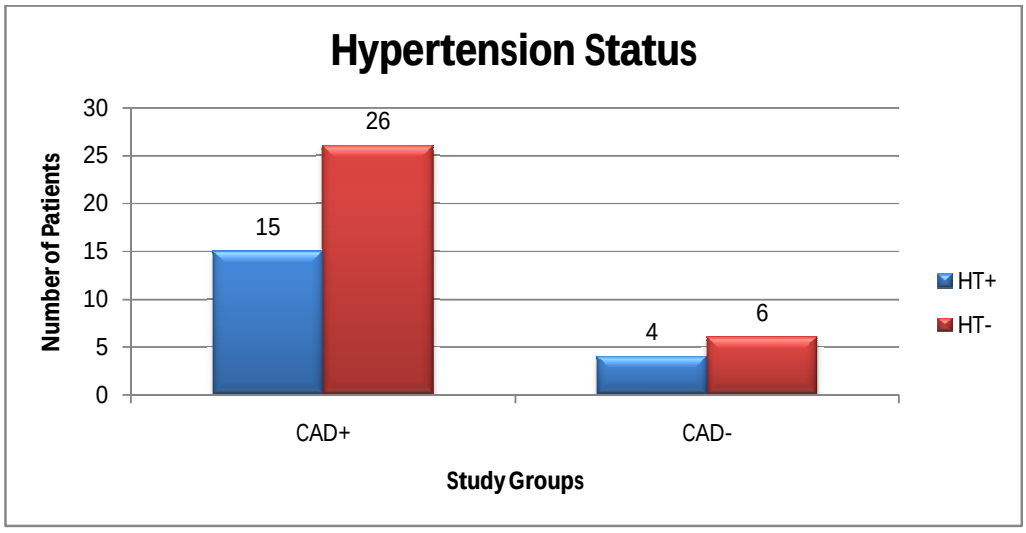
Table – 7 Distribution hypertension in CAD patients

Hypertension Status	CAD+	%	CAD-	%
Hypertensive	15	36.59	4	40
Normal	26	63.41	6	60
Total	41	100	10	100

Table – 8 Diabetes distributions in our study:

Diabetic Status	CAD+	%	CAD-	%
Diabetic	17	41.46	4	40
Normal	24	58.54	6	60
Total	41	100	10	100
P value	**0.9328**			

Hypertension status:



Diabetes in our study:

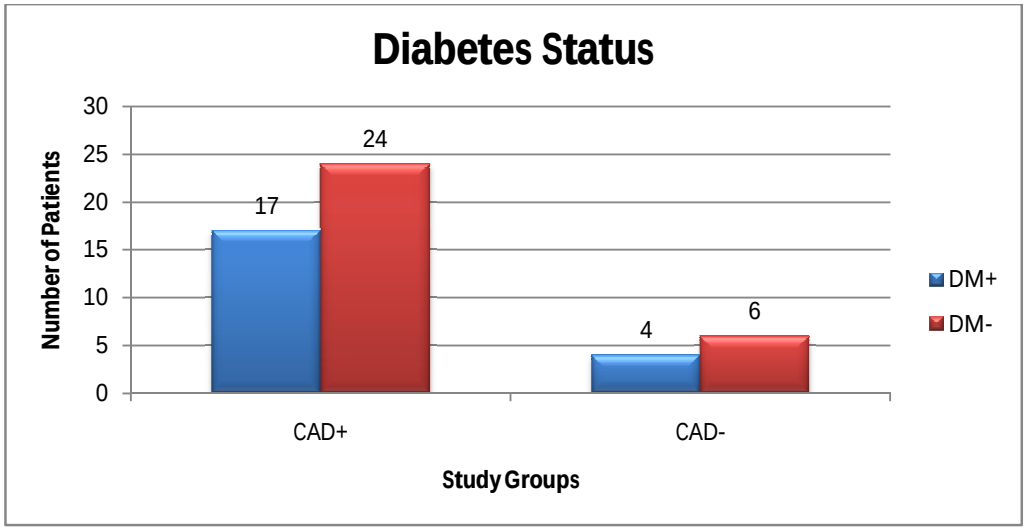


Table – 9 Correlation family history to CAD

Family History of CAD	CAD+	%	CAD-	%
CAD+	17	41.46	1	10
CAD-	24	58.54	9	90
Total	41	100	10	100
P value	**0.0771***			

*significant

Table – 10 LDL distributions in CAD

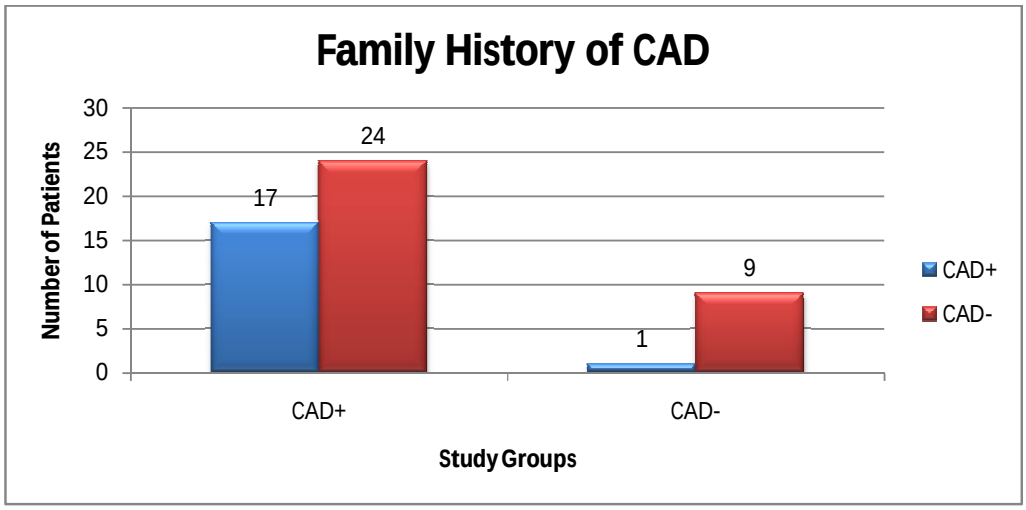
LDL (mg/dl)	CAD+	%	CAD-	%
<100	3	7.32	1	10
100 to 129	10	24.39	6	60
130 to 159	10	24.39	2	20
160 to 199	15	36.59	1	10
>200	3	7.32	0	0
Total	41	100	10	100

Table – 11 Average LDL level correlation to CAD

LDL (mg/dl)	CAD+	CAD-
N	41	10
Mean	152.76	128.50
SD	35.97	22.49
P value	**0.01385***	

*significant

Family history of CAD:



LDL Status:

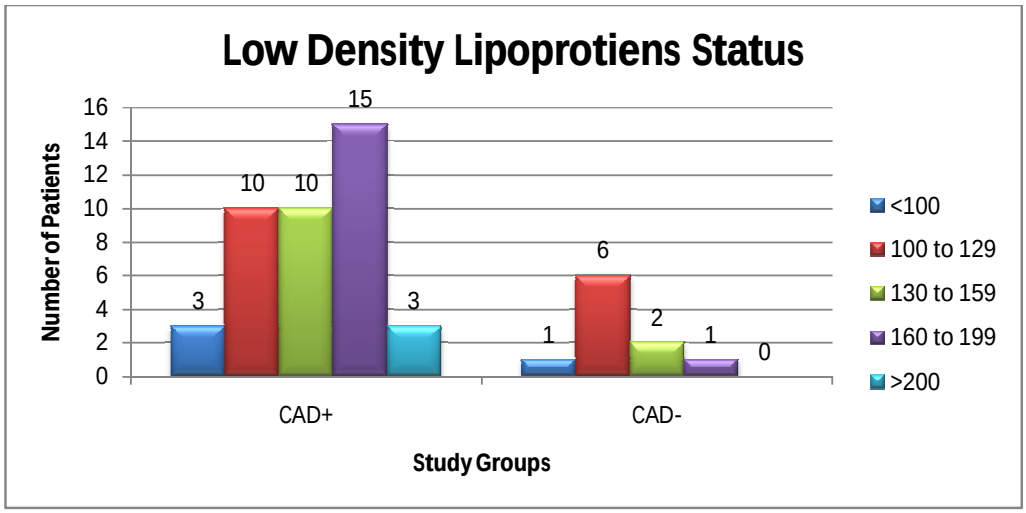


Table – 12 Non HDL level distributions in CAD

Non HDL (mg/dl)	CAD+	%	CAD-	%
<100	0	0	0	0
100 to 129	2	4.88	1	10
130 to 159	10	24.39	6	60
160 to 199	12	29.27	3	30
>200	17	41.46	0	0
Total	41	100	10	100

Table – 13 Average level of Non HDL in CAD

Non HDL (mg/dl)	CAD+	CAD-
N	41	10
Mean	190.49	159.00
SD	42.90	23.33
P value	**0.00398***	

*significant

Non HDL level in the study:

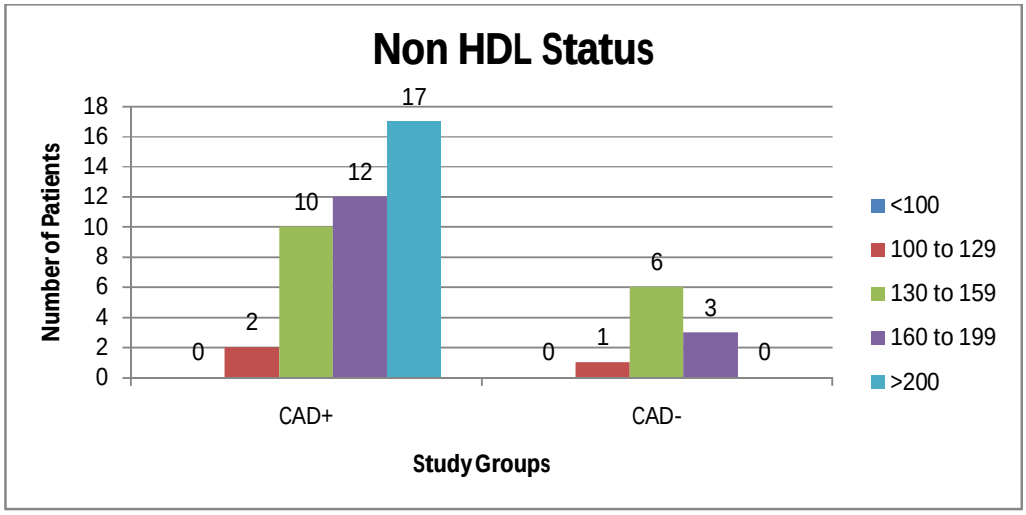


Table – 14 Hemodynamic measurements at rest and peak stress:

Haemodynamic Measurements	CAD+			CAD-			P value
	N	Mean	SD	N	Mean	SD	
Basal HR	41	70.85	10.59	10	72.50	11.89	0.6952
Max HR	41	155.49	16.92	10	165.00	15.10	0.1017
BP Rest Systolic	41	127.07	6.81	10	130.40	6.79	0.1868
BP Rest Diastolic	41	84.12	6.53	10	86.80	4.73	0.1560
BP Peak Systolic	41	164.10	14.68	10	173.20	12.01	0.0566*
BP Peak Diastolic	41	102.49	8.90	10	106.20	11.41	0.3562

*peak systolic BP is significant

Table – 15 Echocardiographic findings at rest:

ECHO Findings	CAD+			CAD-			P value
	N	Mean	SD	N	Mean	SD	
E	41	76.46	17.66	10	87.60	23.36	0.18408
A	41	85.15	20.83	10	103.30	12.84	0.002058*
E/A	41	0.94	0.29	10	0.86	0.30	0.482381
DT	41	215.78	33.21	10	215.80	33.21	0.416758
S' septal	41	6.00	1.22	10	7.74	1.62	0.008127*
E' septal	41	7.87	1.81	10	10.10	2.26	0.013177*
A' septal	41	7.18	1.68	10	8.63	1.66	0.027266*
E/E' septal	41	9.72	1.07	10	8.60	0.82	0.001941*
E'/A' septal	41	1.10	0.18	10	1.18	0.17	0.231774
S' lateral	41	6.84	1.42	10	9.03	1.78	0.00353*
E' lateral	41	8.79	2.15	10	11.39	2.55	0.011101*
A' lateral	41	7,62	2.29	10	9.06	2.15	0.081208
E/E' lat	41	8.78	1.10	10	7.69	1.12	0.014659*
E'/A' lat	41	1.22	0.36	10	1.29	0.36	0.552829
S' inferior	41	5.93	1.17	10	7.59	1.63	0.01092*
E' inf	41	7.97	1.85	10	9.93	2.52	0.039751*
A' inf	41	7.29	1.70	10	8.56	1.59	0.041393*
E/E' inf	41	9.63	1.27	10	8.85	1.19	0.087578
E'/A' inf	41	1.10	0.19	10	1.15	0.16	0.4915
avg S'	41	6.25	1.24	10	8.11	1.63	0.005654*
avg E'	41	8.20	1.87	10	10.47	2.41	0.017041*
avg A'	41	7.37	1.81	10	8.75	1.62	0.032222*
avg E/E'	41	9.37	0.99	10	8.37	0.98	0.011798*

*significant statistically

Table – 16 Echocardiographic findings immediately after TMT:

ECHO Findings	CAD+			CAD-			P value
	N	Mean	SD	N	Mean	SD	
E	41	103.37	22.49	10	111.70	21.28	0.29036
A	41	103.38	21.34	10	98.80	12.26	0.33507
E/A	41	1.01	0.24	10	1.12	0,16	0.09712
DT	41	193.61	442.80	10	181.10	18.50	0.16791
S' septal	41	6.84	1.42	10	9.57	2.07	0.00221*
E' septal	41	8.14	2.16	10	11.98	2.78	0.00159*
A' septal	41	7.83	1.99	10	9.85	2.18	0.01958*
E/E' septal	41	13.15	2.23	10	9.46	1.19	<0.0001*
E'/A' septal	41	1.04	0.15	10	1.21	0.13	0.00227*
S' lateral	41	7.51	1.83	10	10.51	2.21	0.00181*
E' lateral	41	9.02	2.52	10	13.13	3.01	0.00169*
A' lateral	41	8.29	2.37	10	10.01	1.96	0.03013*
E/E' lat	41	11.99	2.12	10	8.64	1.19	<0.0001*
E'/A' lat	41	1.09	0.18	10	1.31	0.17	0.00363*
S' inferior	41	6.84	1.47	10	9.13	1.59	0.00116*
E' inf	41	8.56	2.24	10	22.60	35.36	0.24119
A' inf	41	7.90	1.87	10	9.73	2.04	0.02249*
E/E' inf	41	12.44	2.18	10	9.81	1.37	0.0001*
E'/A' inf	41	1.08	0.16	10	1.16	0.12	0.10892
avg S'	41	7.06	1.49	10	9.74	1.92	0.00147*
avg E'	41	8.58	2.17	10	12.19	2.17	0.00204*
avg A'	41	8.00	2.02	10	9.85	1.95	0.01824*
avg E/E'	41	12.52	1.85	10	9.29	1.21	<0.00001*

*significant statistically

Table – 17 Echo findings difference:

ECHO Findings	CAD+			CAD-			P value
	N	Mean	SD	N	Mean	SD	
E	41	26.90	18.18	10	24.10	7.29	0.44839
A	41	18.68	29.26	10	-4.50	21.74	0.01166*
E/A	41	0.08	0.38	10	0.26	0.25	0.07872
DT	41	-12.17	64.20	10	-34.70	37.55	0.16017
S' septal	41	0.84	0.62	10	1.83	0.80	0.00330*
E' septal	41	0.27	1.24	10	1.88	0.75	<0.0001*
A' septal	41	0.65	1.18	10	1.22	0.82	0.08983
E/E' septal	41	3.43	2.31	10	0.86	1.25	0.0001*
E'/A' septal	41	-0.06	0.23	10	0.03	0.09	0.04658*
S' lateral	41	0.68	0.75	10	1.48	0.55	0.00115*
E' lateral	41	0.23	1.18	10	1.74	0.70	<0.0001*
A' lateral	41	0.67	1.04	10	0.95	1.17	0.49984
E/E' lat	41	3.21	2.04	10	0.95	1.12	0.0001*
E'/A' lat	41	-0.12	0.29	10	0.01	0.23	0.13412
S' inferior	41	0.91	0.59	10	1.54	0.44	0.00143*
E' inf	41	0.60	0.97	10	12.67	35.05	0.30439
A' inf	41	0.60	0.79	10	1.17	0.69	0.03899*
E/E' inf	41	2.81	2.03	10	0.96	1.34	0.00223*
E'/A' inf	41	-0.02	0.15	10	0.02	0.11	0.39922
avg S'	41	0.81	0.51	10	1.63	0.46	0.00017*
avg E'	41	0.38	0.94	10	1.73	0.62	<0.0001*
avg A'	41	0.63	0.84	10	1.10	0.71	0.09305
avg E/A'	41	3.15	1.92	10	0.93	1.21	0.00015*

*significant statistically

Table – 18 Distribution of various categories to TMT positivity and negativity

TMT with Pretest Probability of CAD	TMT+	%	TMT-	%
Low	1	2.63	4	30.77
Intermediate	32	84.21	9	69.23
High	5	13.16	0	0.00
Total	38	100	13	100
P value	**0.007***			

*significant

Table – 19 Distribution of TMT duration and CAD

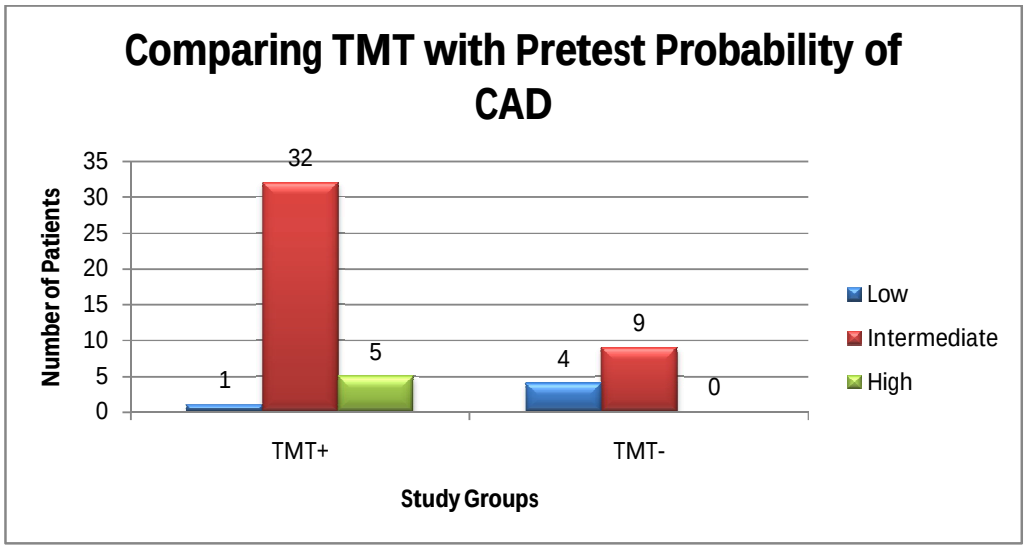
TMT Exercise Duration	CAD+	%	CAD-	%
≤2.5	0	0	0	0
2.6 to 5	15	36.59	0	0
5.1 to 7.5	15	36.59	1	10
7.5 to 10	11	26.83	9	90
Total	41	100	10	100

Table – 20 Correlation of TMT duration with CAD

TMT Exercise Duration	CAD+	CAD-
N	41	10
Mean	6.21	8.68
SD	1.95	0.92
P value	**<0.0001***	

*significant

TMT comparing pre test probability of CAD



Distribution of TMT exercise duration and CAD

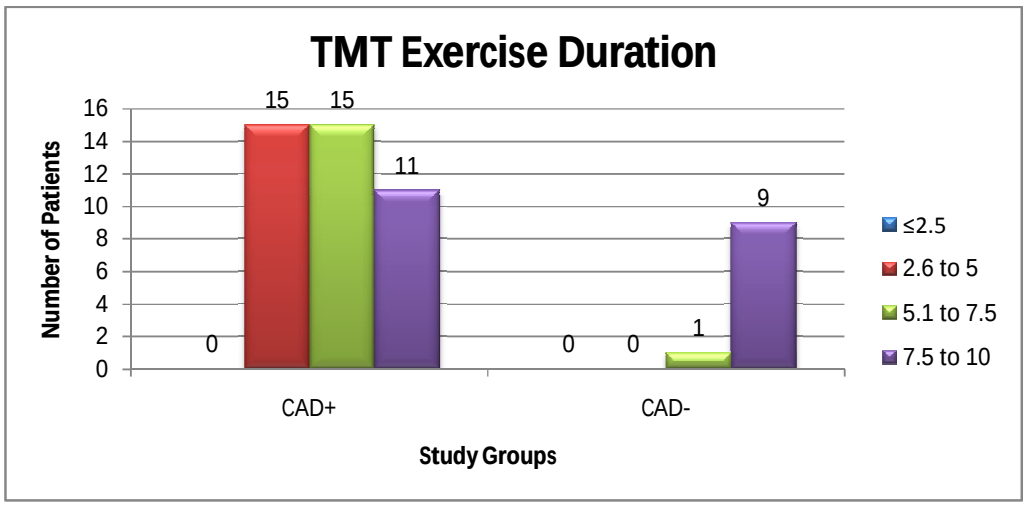


Table – 21 E/E’ correlation with SVD

	SVD+			SVD-			P value
	N	Mean	SD	N	Mean	SD	
Avg E/e' Baseline	38	9.29	1.00	13	8.83	1.18	0.21839
Avg E/e' After Exercise	38	12.18	1.89	13	11.03	2.71	0.178659
Avg E/e' Difference	38	2.88	2.01	13	2.21	1.97	0.300169

Table – 22 DVD correlation with E/E’

	DVD+			DVD-			P value
	N	Mean	SD	N	Mean	SD	
Avg E/e' Baseline	38	9.27	1.03	13	8.88	1.12	0.2808
Avg E/e' After Exercise	38	12.29	2.09	13	10.70	2.00	0.0226*
Avg E/e' Difference	38	3.02	2.07	13	1.82	1.54	0.0353*

*more significant

Table – 23 TVD correlation with E/E’

	TVD+			TVD-			P value
	N	Mean	SD	N	Mean	SD	
Avg E/e' Baseline	38	9.40	1.01	13	8.51	0.94	0.0079*
Avg E/e' After Exercise	38	12.65	1.84	13	9.65	1.32	<0.0001*
Avg E/e' Difference	38	3.25	1.95	13	1.14	1.19	0.0001*

*more significant

Table – 24 Multivariate regression analyses:

Variable	Odds ratio	95% CI	P value
Smoking	1.8261	0.4130 to 8.0745	0.4272
Hypercholesterolemia	15.000	0.8232 to 273.3360	0.0675
Hypertension	0.8645	0.2101 to 3.5652	0.8414
Diabetes	1.0625	0.2595 to 4.3498	0.9328
Positive Treat Mill Exercise Test	1.3286	0.2880 to 6.1286	0.07157
Presence of WMA after exercise	71.8421	3.8448 to 1342.3922	0.0042*
Increase of E/E' average after exercise	3.1667	0.0250 to 10.9591	0.2454

*significant

Table – 25 Correlation of E/E’ to severity of CAD by Gensini score

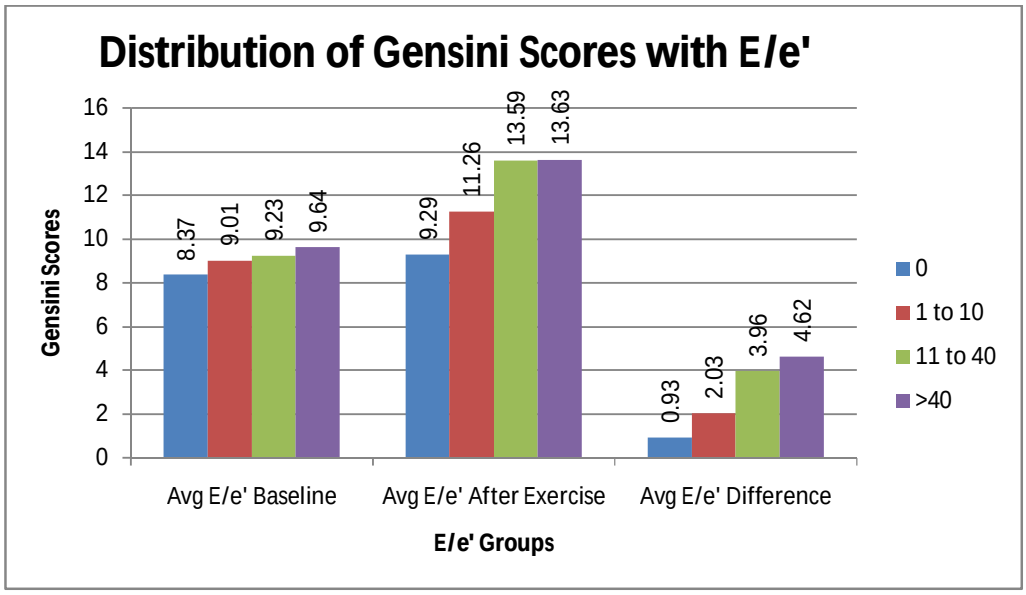
Gensini Score	0			1 to 10			11 to 40			>40			P value
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Avg E/e' Baseline	10	8.37	0.98	19	9.01	0.91	17	9.23	1.06	5	9.64	1.00	0.020649*
Avg E/e' After Exercise	10	9.29	1.21	19	11.26	1.68	17	13.59	1.31	5	13.63	0.74	<0.0001*
Avg E/e' Difference	10	0.93	1.21	19	2.03	1.70	17	3.96	1.68	5	4.62	1.14	<0.0001*

*significant

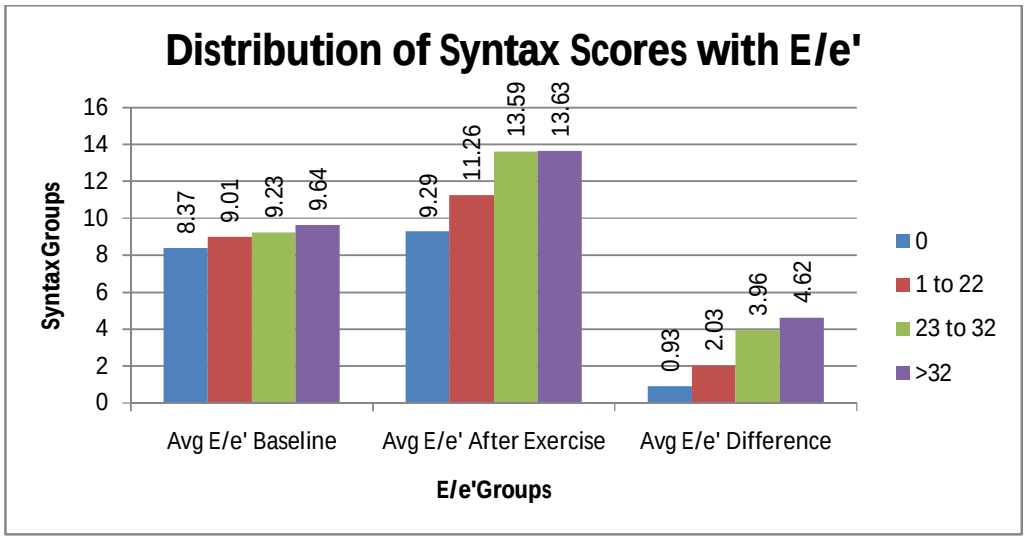
Table – 26 Correlation of E/E’ to severity of CAD by Syntax score

Syntax Score	0			1 to 22			23 to 32			>32			P value
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Avg E/E' Baseline	10	8.37	0.98	34	9.33	0.87	3	10.16	2.19	4	9.09	0.87	0.021013*
Avg E/E' After Exercise	10	9.29	1.21	34	12.17	1.80	3	14.32	1.02	4	14.13	1.02	<0.0001*
Avg E/E' Difference	10	0.93	1.21	34	2.83	1.90	3	4.17	1.91	4	5.04	0.63	0.000709*

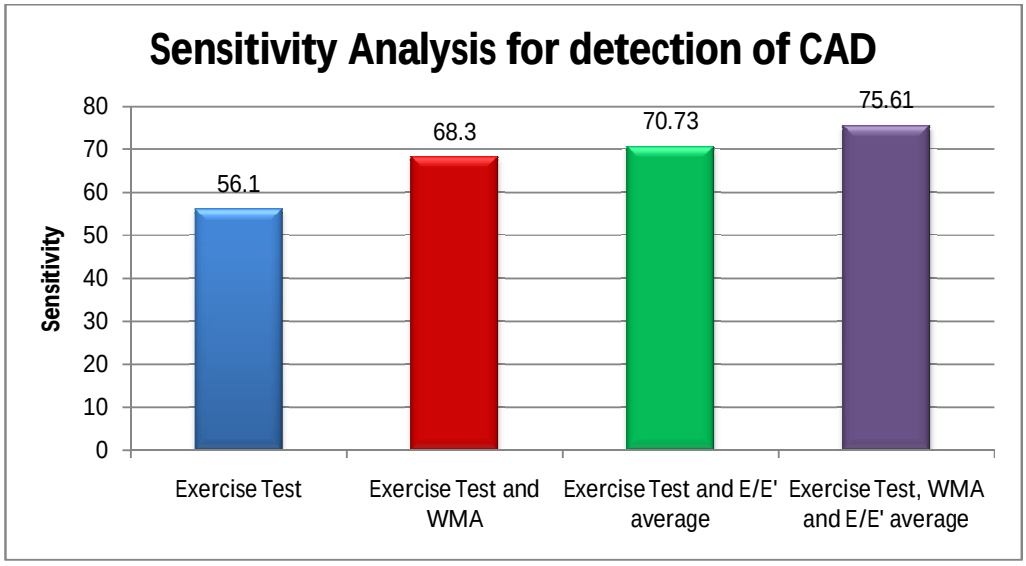
Distribution of E/E’ with Gensini score



Distribution of E/E’ in syntax score



E/E’ Sensitivity for detection of CAD



DISCUSSION

DISCUSSION

In my study we had 51 patients completed all the requirements for analysis out of 72 patients. Seven patients did not undergo various procedures which required for our study and 10 patients echo recordings were suboptimal and two patients with history of old myocardial infarction. In our study 53 years of age is average for coronary artery disease whereas those without CAD were < 50 years. Majority of patients was in our study between 40 to 70 years of age.

Male gender is one of non modifiable risk factor which reflected in our study that 65% diagnosed with CAD whereas female only 34%. Smoking status doesn't carry any statistical significance in our study but 43% were smokers in CAD group. Dyslipidemia is one of the strong predictor of CAD in our study and its average TC associated with CAD was 230 mg% p value 0.013. LDL and NON HDL levels had strong correlation in our study with statistical significance. The CAD positive patients had average LDL of 153 mg/dl than 128 mg/dl for without CAD. The NON HDL level of 190 mg/dl had good correlation to CAD than 159 mg/dl for without CAD. Hypertensive patients in our study are low because we included only grade I hypertension in our study. It doesn't show any correlation to CAD. The baseline systolic BP in both groups were almost equal (130 mmhg) both groups. We had 21 patients with diabetes;

majority 17 out of 21 had CAD. Patients with h/o CAD in family had higher chances of CAD which correlated significantly. Patients with coronary artery disease had lower peak systolic BP during TMT than others (164 vs 173), which has p value of 0.0566. And the peak HR also 10 beats/min is less in CAD group than non CAD group but did not correlate significantly. Baseline TDI systolic velocity (S') was lower in CAD patients than without CAD (6.25 vs 8.11 cm/sec) which shown in other studies. Our study had lower E' and A' in patients with coronary artery disease. But E/E' slightly higher than normal value in CAD group (9.37 vs 8.37). Tissue Doppler systolic velocity for different segments in baseline mainly basal septal, basal lateral and basal inferior are 8.11, 10.47 and 8.75 cm/sec respectively. There were significant changes tissue Doppler echo parameters in patients with CAD after stress test. The systolic velocity did not increase after stress test in patients with coronary artery disease.

Baseline Tissue Doppler average early and late diastolic velocity in our study is 10.47 cm/sec and 8.37 cm/sec. The diastolic parameters E prime and A prime was not competitively increased in CAD group. But there was decrease in E velocity and increase in A velocity as occur in other studies. Average E/E' ratio of all three myocardial segments measured is significantly increased and the increasing change (3.15) well correlated with CAD detection in diastolic stress test.

The average increase in E/E’ ratio well correlated in patients with positive TMT. Duration of exercise time is low in patients with CAD than without CAD (6.21 vs 8.68 min). Patients with negative TMT and normal CAG higher exercise capacity, peak systolic pressure, low LDL, low NON HDL, normal S’ velocity and same E/E’ ratio before and after stress. The increase in E/E’ ratio did not correlate with SVD but well correlated with double vessel disease and triple vessel disease. The p value of our study was significant in univariate analysis but was not significant in multivariate analysis

When patients were divided into four subgroups according to Gensini scores and compared with Average E/E' Baseline/ Average E/E' After Exercise/ change in Average E/E', all these parameters incrementally increased as Gensini score increased. There is a statistically significant correlation between E/e’ groups and Gensini scores (Average E/E' Baseline – p=0.020649, Average E/E' After Exercise – p=0.0000 and Average E/E' Difference – p=0.0000).In simple terms we can conclude that E/E’ is an independent predictor of severity and extension of coronary stenosis as indicated by Gensini scores. The same time Syntax scores compared with Average E/E' Baseline/ Average E/E' After Exercise/ change in Average E/E', all these parameters incrementally increased as

Syntax score increased. There is a statistically significant correlation between E/E’ groups and Syntax scores (Average E/e' Baseline – p=0.021013, Average E/E' After Exercise – p=0.0000 and Average E/E' Difference – p=0.000709). In simple terms we can conclude that E/E’ is an independent predictor of complexity of coronary artery disease as indicated by Syntax scores

In our study TMT positive had 56% sensitivity for detection of CAD, but it is around 68% in tsougos study, when combining increase in E/E’ value with stress echocardiography its sensitivity rose to 71%. Moreover including objective measurement of wall motion abnormalities with other parameters sensitivity for detection of CAD as high as 75% in our study, but tsougos et demonstrated that combining all the above parameters sensitivity was 97%. Our study did not reach 97% sensitivity due to various factors which is mentioned in study limitations. Still it increases sensitivity to detect coronary artery disease. It needs further study with larger population to decide E/E’ as sensitive marker to diagnose CAD.

STUDY LIMITATIONS

LIMITATIONS OF STUDY

1. TDI measurements are time consuming and there may be change in parameters if recorded later than 1-2 mins after completion of TMT

2. There is overlapping of waveforms during tachycardia and difficulty in measurements

3. During velocity calculation the motion of measuring segments may be altered by adjacent scarred or normal segments.

4. Our study was looking at patients mainly with intermediate pre test probability of CAD, where patients are younger than others studies.

CONCLUSION

CONCLUSION

1. The systolic velocity S' is reduced in patients with obstructive CAD
2. The average E/E' ratio in Indian population during rest without CAD is 8.37 but slightly increased in CAD patients (9.37)
3. There is significant reduction of all diastolic parameters E', A' with stress test noted in patients with CAD
4. A significant increase in E/E' ratio (3.15 $\pm$ 1.92) from baseline irrespective of baseline value during stress test highly correlated with presence of obstructive CAD.
5. The baseline and stress E/E' ratio incrementally increased as severity of CAD increases.
6. Post treadmill exercise echocardiography using TDI to measure E/E' ratio increases sensitivity of CAD detection form 56% to 71% in our study.

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ANNEXURES

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work	: Diastolic stress test –Novel marker to detect coronary Artery disease - A Tissue Doppler echocardiographic study
Principal Investigator	: Dr.S. Rajesh Kumar
Designation	: PG in D.M (Cardio)
Department	: Department of Cardiology Government Stanley Medical College, Chennai-10

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 08.11.2013 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

20/1/14

MEMBER SECRETARY,
IEC, SMC, CHENNAI

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File size:	959.21K
Page count:	68
Word count:	11,008
Character count:	53,075
Submission date:	23-Mar-2014 09:05PM
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INTRODUCTION

Coronary artery disease (CAD) is one of the leading cause of morbidity and mortality in the world and has nearing its epidemic proportions. Coronary artery disease causes 9.4 percent of total deaths (25 lakhs) in under developed countries and 16.3 percent (13 lakhs) of all deaths in developed countries[1]. The world health organisation (WHO) has calculated the year of 2002 alone, 12.6 percent of deaths in the world were because of CAD[2]. The proportion of CAD is expected to increase as it is disease of aging and the world population getting older.

The India has similar scenario, Indian studies has revealed that cardiovascular diseases (CVD) cause about 40% of deaths in the urban areas and 30% of deaths in rural areas in india[3]. Prevalence of cardio vascular disease in the adult population has multiplied in urban areas from around 2% in early 1960's to 6.5% in late 1970's, 7% during the year 1980, to close 10 % in 1990 and to a critical 10.5% in the year 2000, the same time in rural areas, it is increased to a smaller extent from about 2% during 1970, to 2.5% in late 1980's , and to calculated 4% in the 1990, at last the prevalence has reached 4.5% in 2000.

So prevention of cardiovascular diseases among people is more important, if cardiovascular disease occurs the earlier detection and

PROFORMA

Name: **Age:** **Sex:**

Occupation: **DOA:** **IP NO:** **CD NO**

Address:

Mobile no;-

Diagnosis:

History: 1. Chest pain -typical/atypical 2. Dyspnea –NYHA class- 3.Others

Risk Factors:

Male Gender: DM: Smoking: Dyslipidemia: HTN: F/H of CAD:

Drug therapy

Examination:

Vitals: - pulse: BP: SpO2:

Hieght: Weight: BMI:

W/H ratio:

CVS: RS:

CXR- PA view:

ECG:

TMT: Protocol- Bruce/modified Bruce

Basal HR - Max HR - APMHR –

BP at REST - BP at PEAK exercise -

Total duration of exercise- METs-

Reason to stop - positive/inconclusive/negative

ECHO:

IVSd / IVSs: LVIDd: AO/LA diameter (M mode):

LV PWd/ PWs: LVIDs:

EF (TEICHOLZ):

RWMA:

	Before exercise	After exercise
LAD territory		
LCX territory		
RCA territory		

Mitral valve: Aortic valve: Tricuspid valve:

PHT

Diastolic dysfunction:

	Before exercise	After exercise
E		
A		
E/A		
DT		

Tissue Doppler velocity:

TDI- velocity m/sec	Before exercise				After exercise			
	Septal	Lateral	Inferior	Avg	Septal	Lateral	Inferior	avg
S’								
E’								
A’								
E/E’								
E’/A’								

RA/RV function: pericardial effusion:

INVESTIGATIONS

Hb: RBS: UREA: CREATININE: ELECTROLYTES - NA/K:

CPK: CPK-MB: Troponin-T:

LIPID PROFILE: T.CHOLESTEROL: TGL: LDL: HDL:

Non HDL:

CARDIAC CATHETERIZATION:

Coronary angiogram:

Gensini score:

Syntax score:

Consent Form

I agree to participate in the study titled - "Diastolic stress test- Novel marker to detect coronary artery disease A Tissue Doppler echocardiography study"

I confirm that I have been told about this study in my mother tongue and have had the opportunity to ask question.

I understand that my participation is voluntary and I may refuse to participate at any time without giving any reason and without affecting my benefits.

I agree not to restrict the use of any data or results that arise from the study.

I agree to undergo the necessary investigation which is part of the study.

Name of the participant:

Signature / thumb impression:

Investigator:

நோயாளிகளுக்கான ஆலோசனை

j‹wd; Cf;f‹a bkyþyhy‹ , ja Ma;t[khu ilg;ig fz¡Lg‹of;Fk; g[j‹a nrhjid Kiw/ jir bkyþyhy‹ , ja Ma;t[பற்றி நான் ஒரு ஆய்வு மேற்கொண்டு உள்ளேன்.

இந்த கண்காணிக்கப்பட்ட மருத்துவ ஆய்விற்கு தாங்களும் பதிவு செய்து தங்களது முழு ஒத்துழைப்பை நல்குமாறு தங்களை அன்புடன் கேட்டுகொள்கிறேன் .

நோயாளிகள் ஒப்புதல்

இந்த இருதய உட்புகுத்து பரிசோதனை / **j‹wd; Cf;f‹a , ja kd¡diy tiut[/ j‹wd; Cf;f‹a bkyþyhy‹ , ja Ma;t[**பற்றி விளக்கப்பட்டது. இதனால் ஏற்படகூடிய பக்க விளைவுகள் பற்றி மருத்துவரின் மூலம் தெரிந்துகொண்டேன்.

பரிசோதனை மற்றும் நடத்தப்படும் ஆய்வை பற்றி முழுமையாக மருத்துவர் விளக்கினார். நான் இந்த ஆய்வில் பங்கெடுக்க முழு மனதுடன் சம்மதம் தெரிவிகின்றேன் .

நோயாளியின் கையொப்பம்

ஒப்புதல் படிவம்

j‹wd; Cf;f‹a bkyþyhy‹ , ja Ma;t[khu i lg;ig f z¡L g‹of;Fk; g[j‹a nrhj id Kiw/ j i r bkyþyhy‹ , j a Ma;t[

நோயாளியின் ஒப்புதல் படிவம்

ஆராய்ச்சி நிலையம் : அரசு ஸ்டான்லி மருத்துவமனை, சென்னை 600001

பங்கு பெறுபவரின் பெயர் :

பங்கு பெறுபவரின் கையொப்பம் :

பங்கு பெறுபவர் இதனை ( ) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது .

நான் இந்த ஆய்வில் தன்னிச்சையாகத்தான் பங்குபெருகிரேன் .எந்த காரணத்தினாலோ எந்த சட்டசிக்கல்களுக்கும் உட்படாமல் நான் இந்த ஆய்வில் இருந்து விலகிக்கொள்ளலாம் என்று அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற் கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்துகொள்கிறேன்.நான் ஆய்வில் இருந்து விலகிக்கிகொண்டாலும் இது பொருந்தும் என அறிந்தேன்.

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும் , பரிசோதனை முடிவுகளையும், மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட அறிவுரைகளின் படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதி அளிகின்றேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத, வழக்திர்க்குமாறன நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணிக்கு தெருவிப்பேன் என உறுதி அளிக்கிறேன்.

இந்த ஆய்வில் எனக்கு ரத்தம், சிறுநீர், எக்ஸ்ரே, ஸ்கேன், உட்பட அனைத்து பரிசோதனைகளையும் செய்து கொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம்..... .....இடம்.....தேதி .....

கட்டைவிரல் ரேகை.....

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

.....

ஆய்வாளரின் கையொப்பம்..... ..இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....